# NEOPLASIA

## Dr. PRIYANKA SACHDEV, MD

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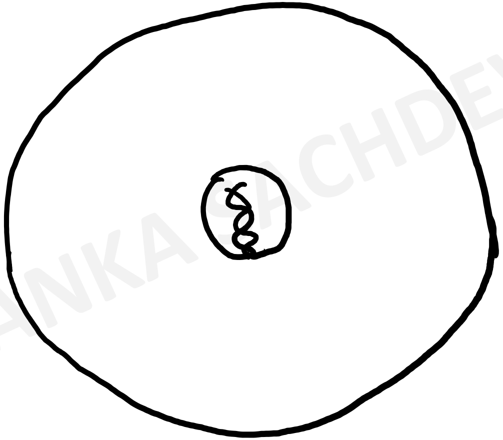
# DEFINITION

- The term ‘neoplasia’ means **new growth**
- The new growth produced is called ‘**neoplasm**’ or ‘**tumour**`
- The branch of science dealing with the study of neoplasms is called **oncology**

# Normal Cell



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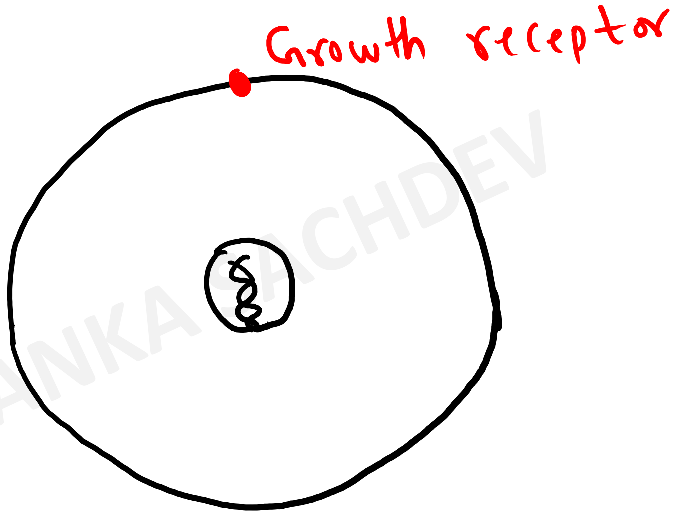
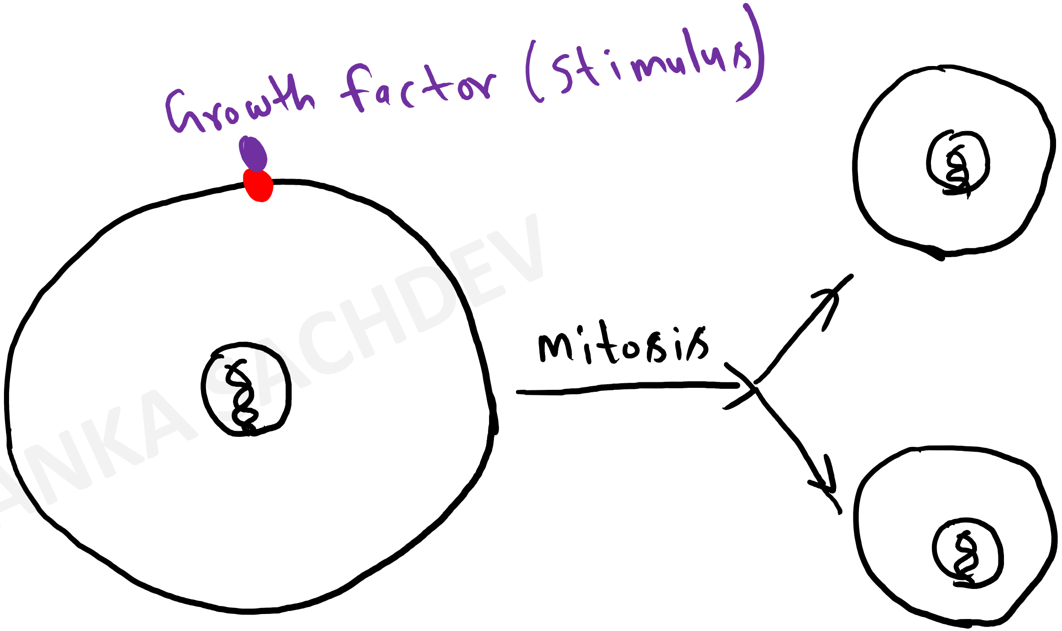
# Normal Cell


Growth receptor

# Normal Cell


Growth factor (stimulus)
mitosis

- “**A neoplasm** is an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissues and persists in the same excessive manner even after cessation of the stimuli which evoked the change.”

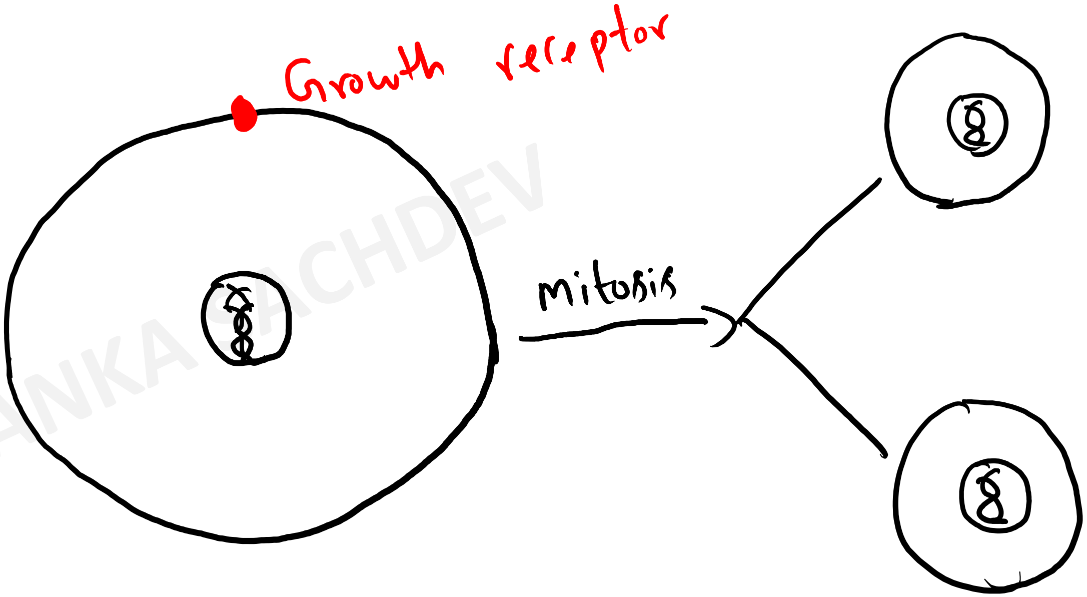
# Neoplasm

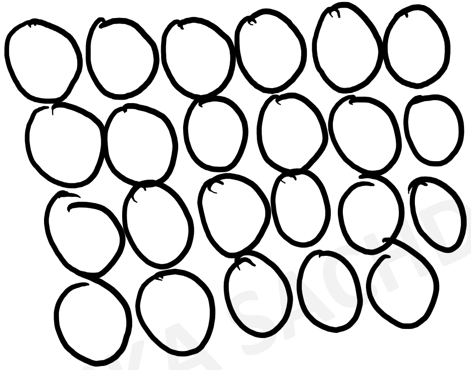
**An abnormal mass of tissue**

- The growth of which **exceeds and is uncoordinated** with that of the normal tissues
- Persists in the same excessive manner **even after cessation of the stimuli** which evoked the change.

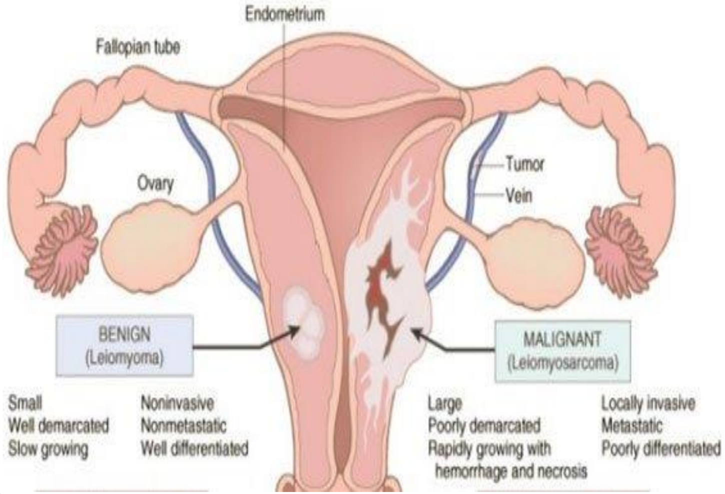
# Neoplastic Cell

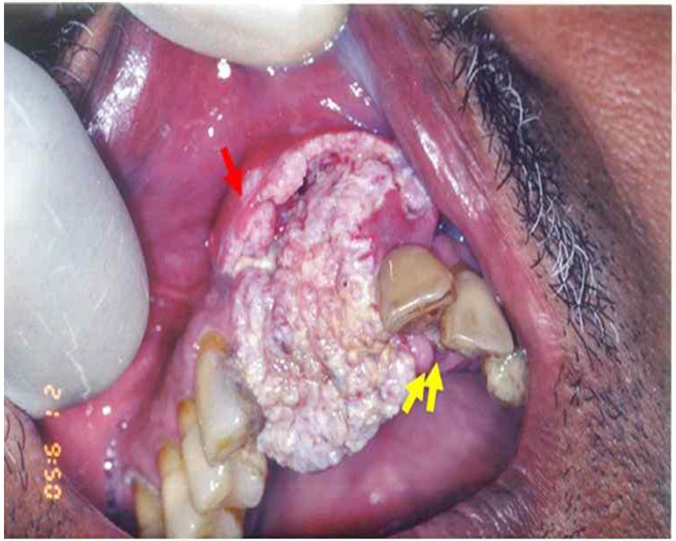
## Absence of Growth Factor (Stimulus)


Growth receptor
mitosis



Neoplasm


Endometrium
Fallopian tube
Ovary
Tumor
Vein
BENIGN (Leiomyoma)
MALIGNANT (Leiomyosarcoma)
Small
Well demarcated
Slow growing
Noninvasive
Nonmetastatic
Well differentiated
Large
Poorly demarcated
Rapidly growing with hemorrhage and necrosis
Locally invasive
Metastatic
Poorly differentiated



# Genetic regulators (genes)

**Normal cell growth,** 4 regulatory genes:

i) **Proto-oncogenes** are growth-promoting genes

ii) **Anti-oncogenes or tumour suppressor genes** are growth-inhibiting or growth suppressor genes.

iii) **Apoptosis regulatory genes** control the programmed cell death.

iv) **DNA repair genes** regulate repair of DNA damage that has occurred during mitosis and also control the damage to proto-oncogenes and antioncogenes.

# Genetic regulators (genes)

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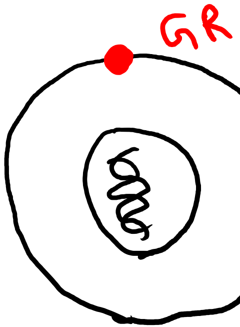
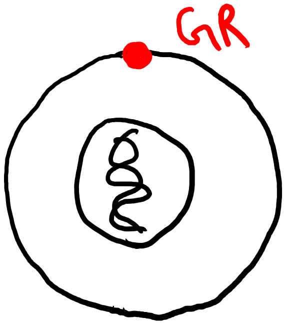
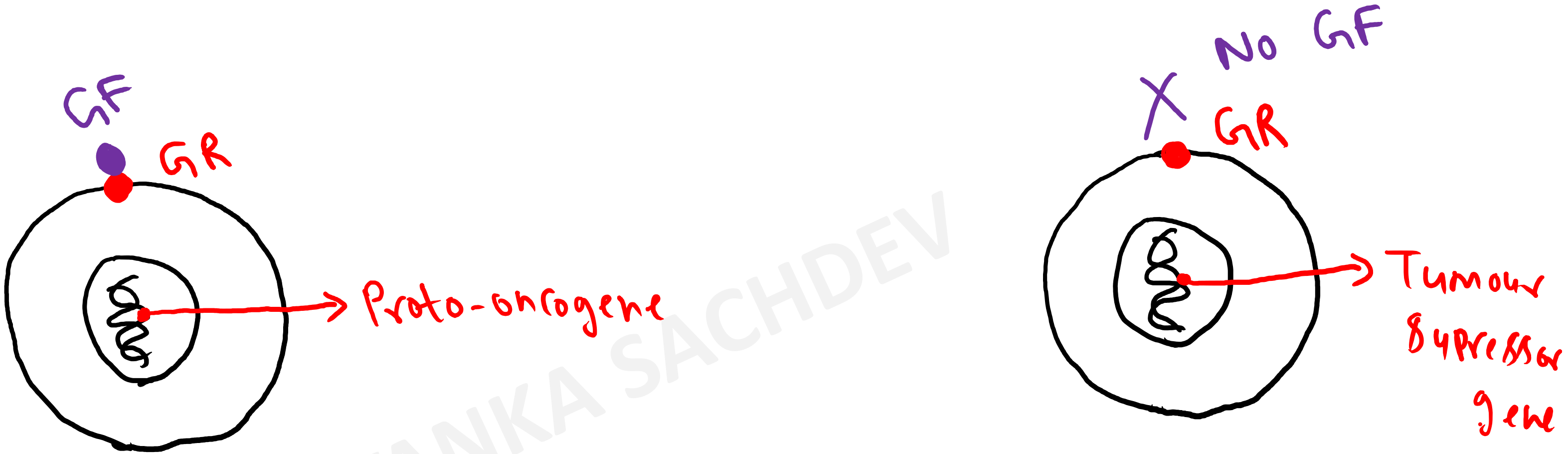
ii) **Anti-oncogenes or tumour suppressor genes** are growth-inhibiting or growth suppressor genes.

# NORMAL CELL

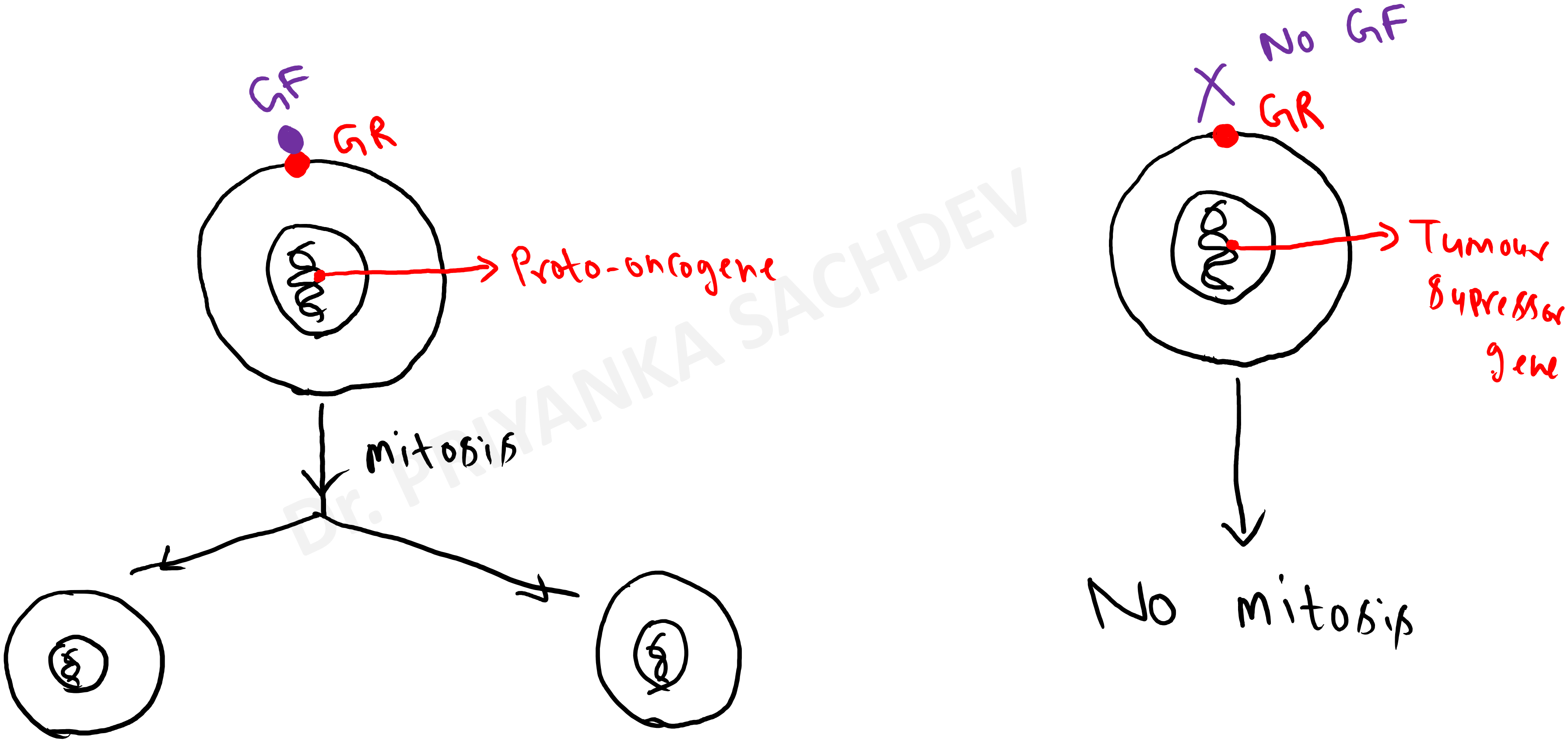




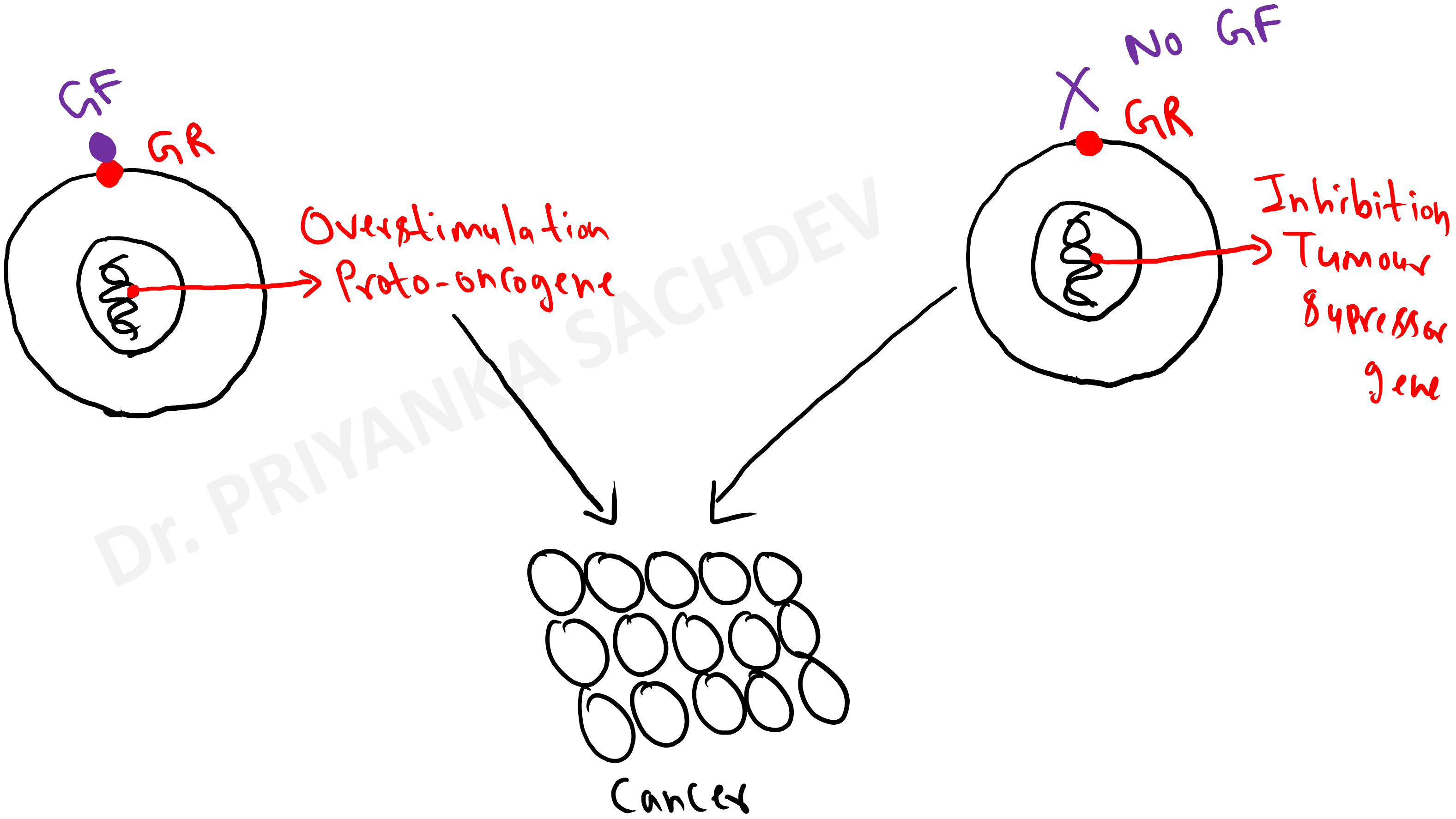
# NORMAL CELL


GF
GR
Proto-oncogene
X No GF
GR
Tumour Suppressor gene

# NORMAL CELL


GF
GR
Proto-oncogene
mitosis
No GF
GR
Tumour suppressor gene
No mitosis

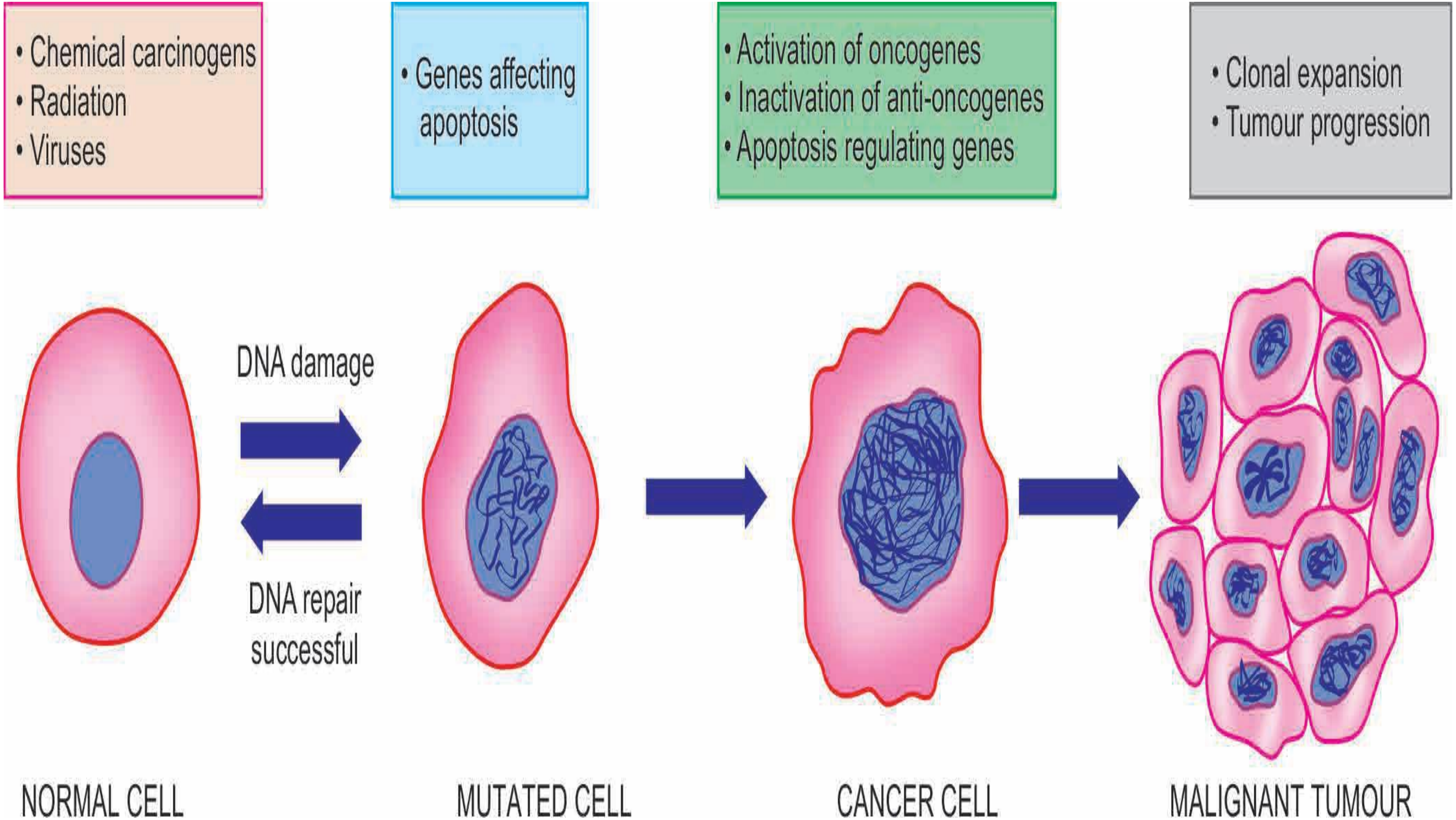
# NORMAL CELL


GF
GR
Overstimulation
Proto-oncogene
No GF
GR
Inhibition
Tumour
Suppressor
gene
Cancer

# In cancer

i) Overstimulation of proto-oncogenes

ii) Inhibition of tumour-suppressor genes



- Chemical carcinogens
- Radiation
- Viruses

- Genes affecting apoptosis

- Activation of oncogenes
- Inactivation of anti-oncogenes
- Apoptosis regulating genes

- Clonal expansion
- Tumour progression

DNA damage

DNA repair successful

NORMAL CELL

MUTATED CELL

CANCER CELL

MALIGNANT TUMOUR

# In cancer

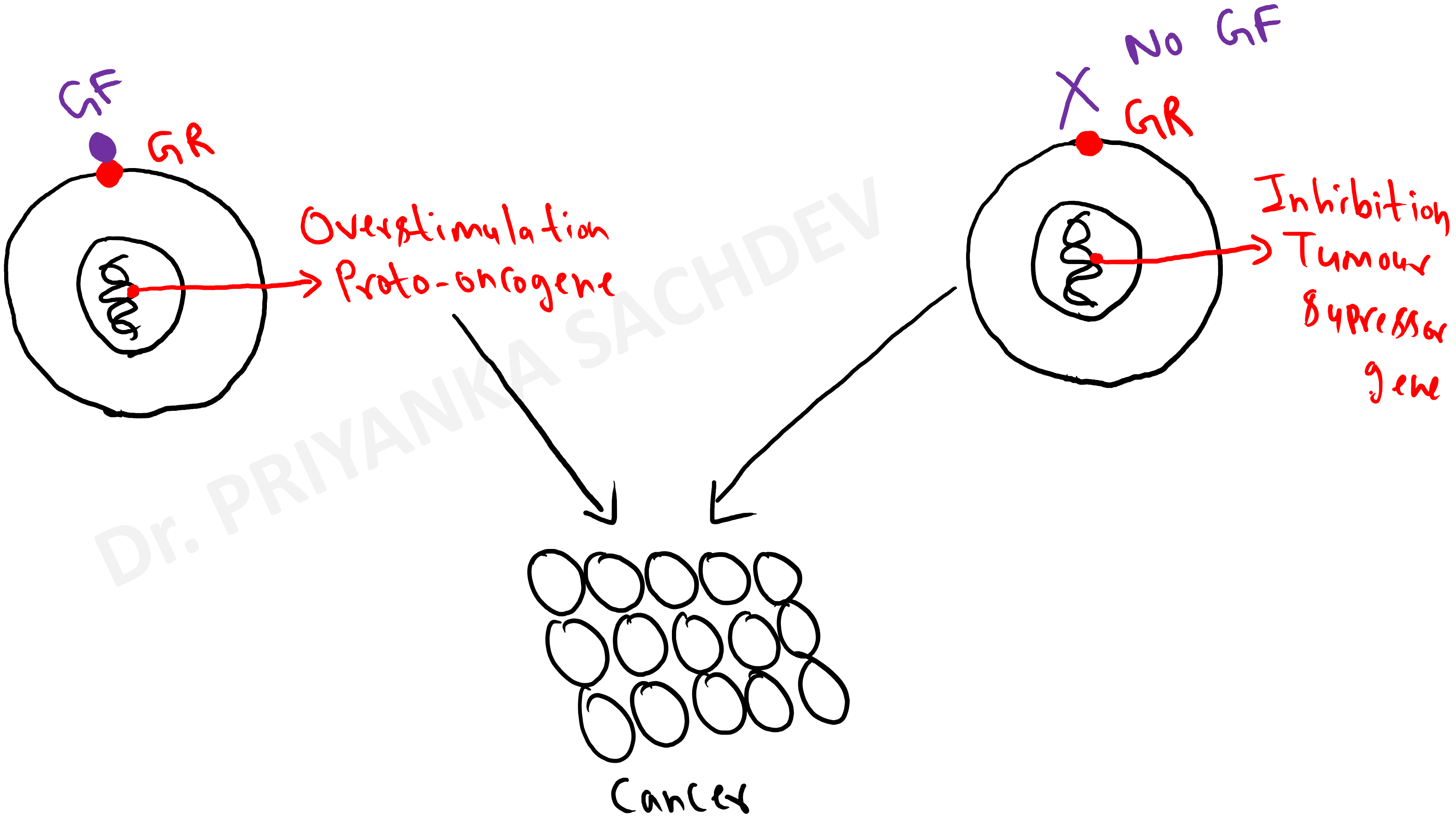
i) Overstimulation of proto-oncogenes

ii) Inhibition of tumour-suppressor genes

# Activation of Proto-Oncogenes

Like us

# NORMAL CELL


GF
GR
Overstimulation
Proto-oncogene
No GF
GR
Inhibition
Tumour Suppressor gene
Cancer

# Proto-oncogenes

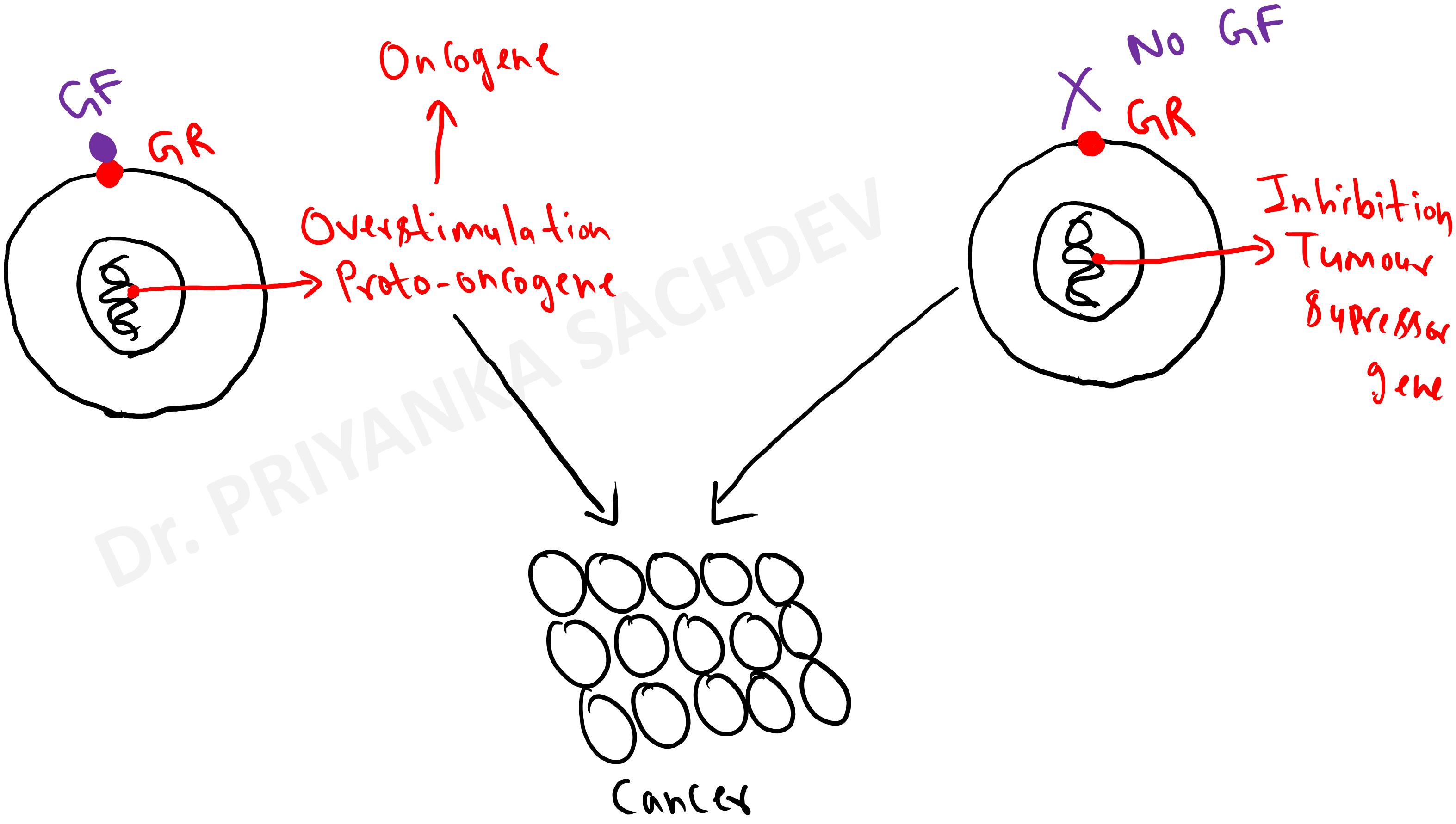
- Proto-oncogenes were discovered by **Harold Varmus and Michael Bishop.**

- **Normal genes** required for cell proliferation
- They act under proper **physiological stimuli**
- Without physiological stimuli they will be silent and there is no replication.

# Oncogenes

- **Derived from mutation of proto-oncogenes**
- 
- When, due to mutation, proto- oncogenes become autonomous ie. promote cell growth **without any physiological stimulus,** it acts as oncogene.

# NORMAL CELL


GF
GR
Oncogene
Overstimulation
Proto-oncogene
No GF
GR
Inhibition
Tumour
Suppressor
gene
Cancer

- Infact oncogene and protooncogene is the same,

- In normal cell it acts as protooncogen while in cancer cell it acts as oncogene

**Proto-oncogenes** (Normal genes required for cell proliferation and differentiation)

↓ Mutation

**Oncogenes** (Genes promoting autonomous cell growth in cancer cells)

↓

**Oncoproteins** (Proteins lacking regulatory control and responsible for promoting cell growth)

Transformation of **proto-oncogene to oncogene** occur by 3 mechanisms:

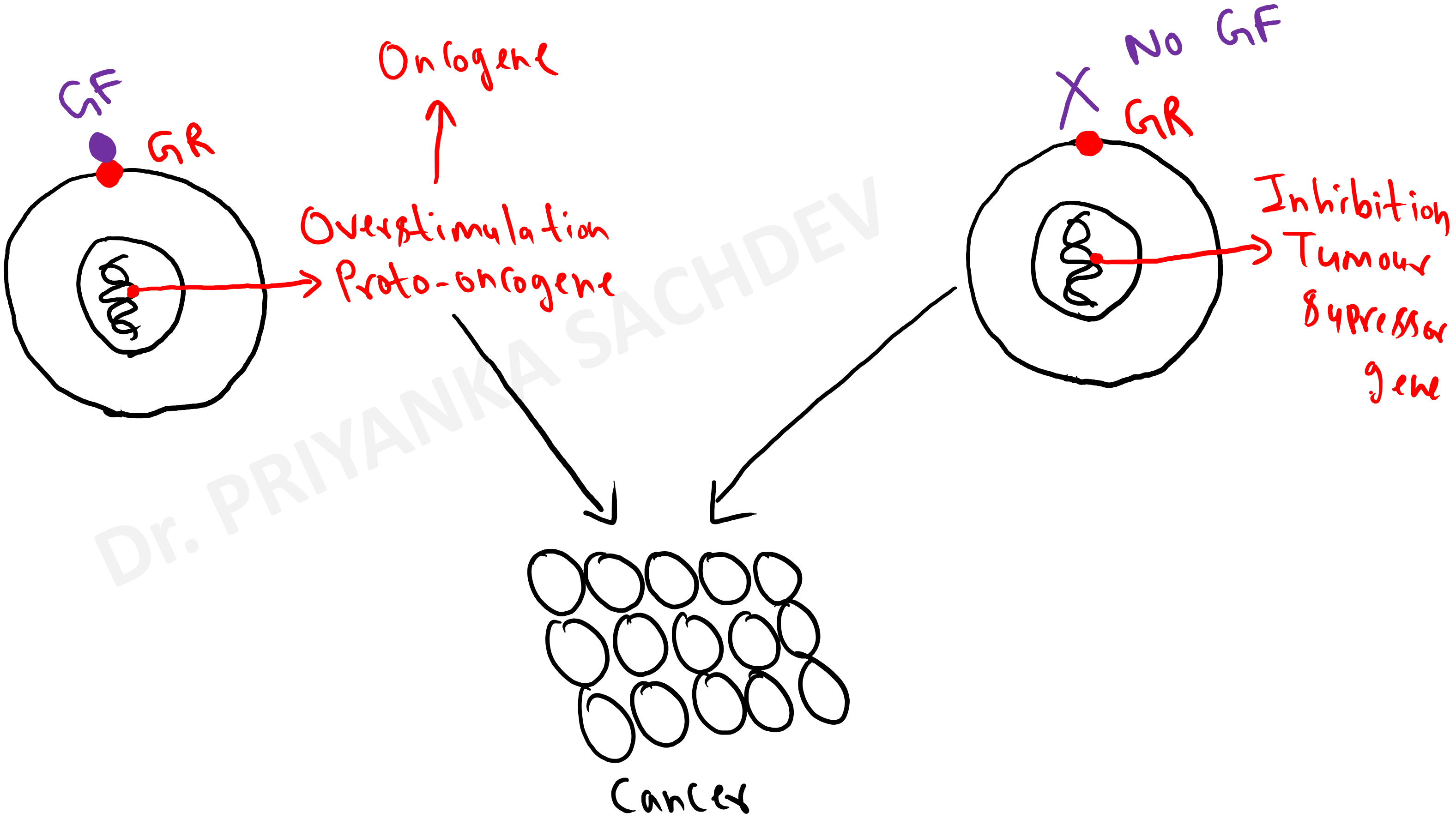
- **Point mutations**
- **Chromosomal translocations**
- **Gene amplification**

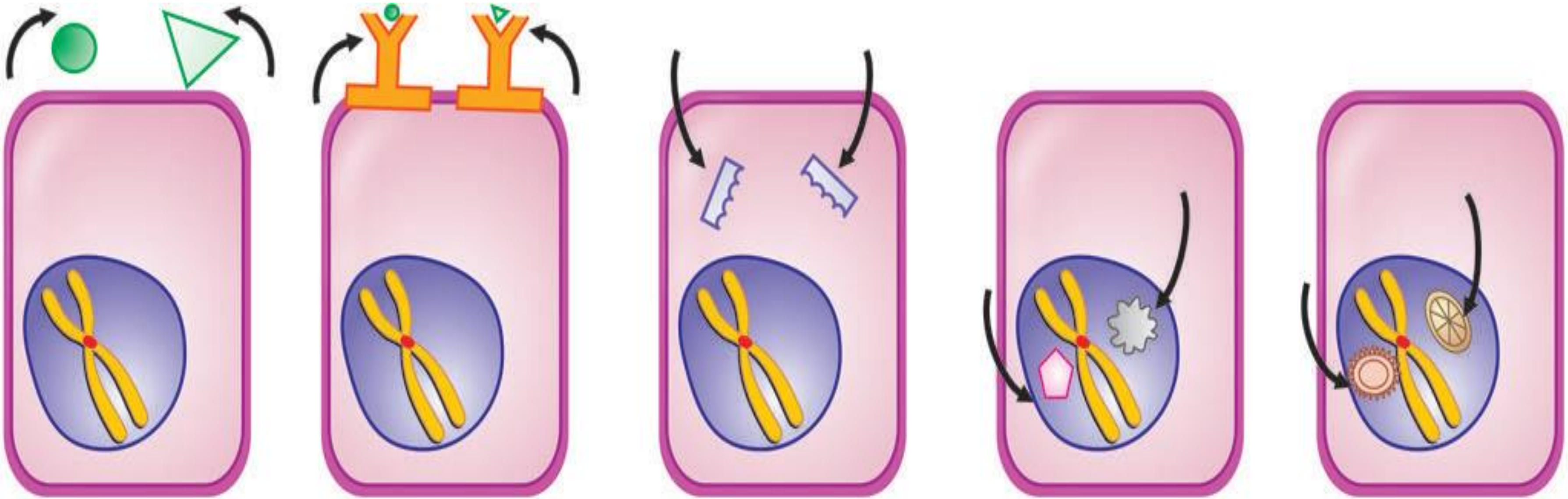
# CLASSIFICATION

**5 classes→**

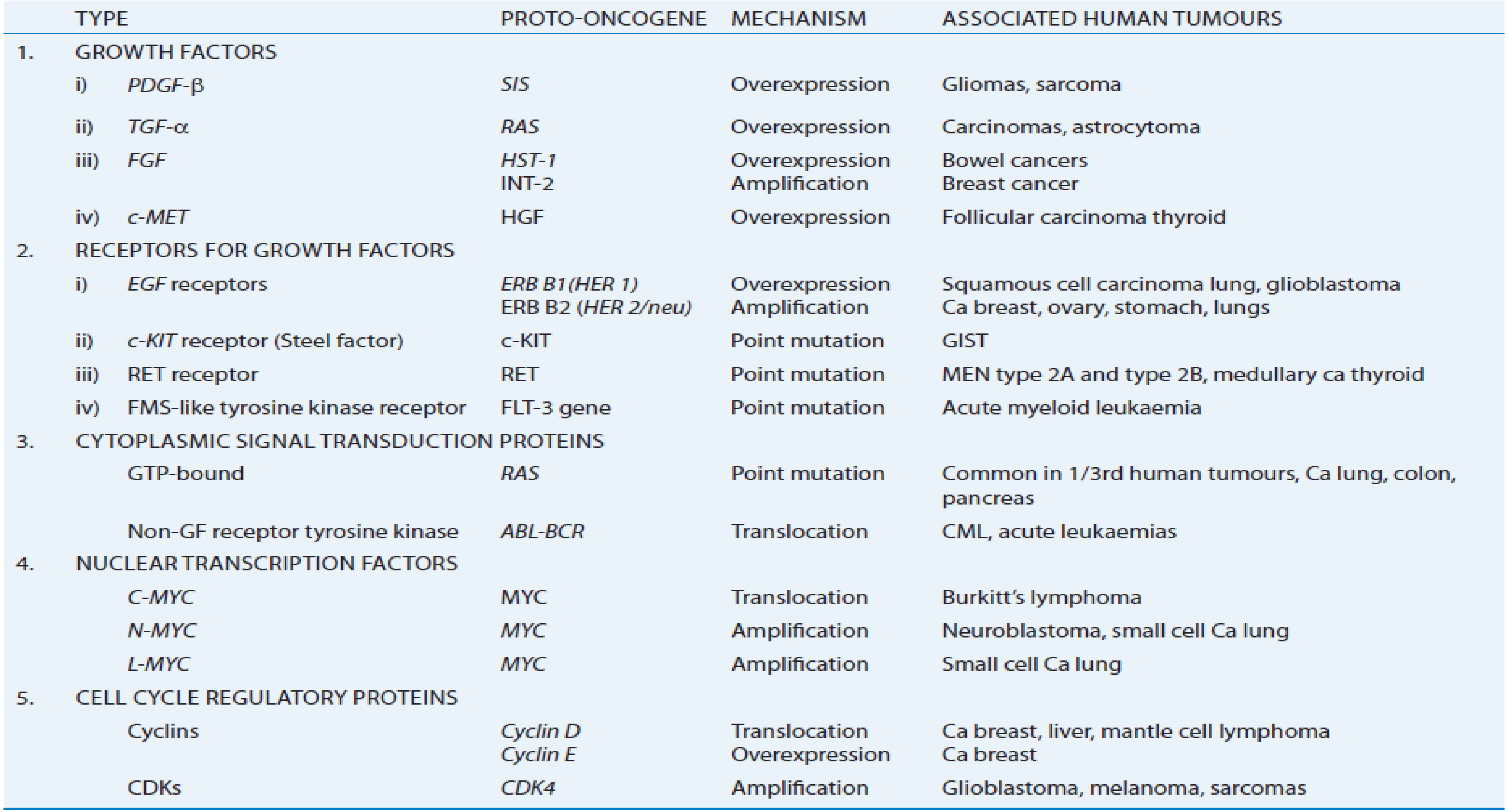
- i) Growth factors
- ii) Receptors of growth factors
- iii) Cytoplasmic signal transduction proteins
- iv) Nuclear transduction factors
- v) Cell regulatory proteins

# NORMAL CELL


GF
GR
Oncogene
Overstimulation
Proto-oncogene
X
No GF
GR
Inhibition
Tumour
Suppressor
gene
Cancer



| GROWTH FACTORS | RECEPTORS FOR GFs | CYTOPLASMIC SIGNAL TRANSDUCTION PROTEINS | NUCLEAR TRANSCRIPTION FACTORS | CELL CYCLE REGULATORY PROTEINS |
|---|---|---|---|---|
| i) PDGF-β<br>ii) TGF-α<br>iii) FGF<br>iv) c-MET | i) EGF-R<br>ii) c-KIT -R<br>iii) RET-R<br>iv) FMS-like | I) Mutated RAS<br>ii) ABL-BCR | i) C-MYC<br>ii) N-MYC<br>iii) L-MYC | i) Cyclin D<br>ii) Cyclin E<br>iii) CDK4 |



| | TYPE | PROTO-ONCOGENE | MECHANISM | ASSOCIATED HUMAN TUMOURS |
|---|---|---|---|---|
| 1. | GROWTH FACTORS | | | |
| | i) *PDGF*-β | *SIS* | Overexpression | Gliomas, sarcoma |
| | ii) *TGF*-α | *RAS* | Overexpression | Carcinomas, astrocytoma |
| | iii) *FGF* | *HST-1* | Overexpression | Bowel cancers |
| | | INT-2 | Amplification | Breast cancer |
| | iv) *c-MET* | HGF | Overexpression | Follicular carcinoma thyroid |
| 2. | RECEPTORS FOR GROWTH FACTORS | | | |
| | i) *EGF* receptors | *ERB B1(HER 1)* | Overexpression | Squamous cell carcinoma lung, glioblastoma |
| | | ERB B2 (*HER 2/neu)* | Amplification | Ca breast, ovary, stomach, lungs |
| | ii) *c-KIT* receptor (Steel factor) | c-KIT | Point mutation | GIST |
| | iii) RET receptor | RET | Point mutation | MEN type 2A and type 2B, medullary ca thyroid |
| | iv) FMS-like tyrosine kinase receptor | FLT-3 gene | Point mutation | Acute myeloid leukaemia |
| 3. | CYTOPLASMIC SIGNAL TRANSDUCTION PROTEINS | | | |
| | GTP-bound | *RAS* | Point mutation | Common in 1/3rd human tumours, Ca lung, colon, pancreas |
| | Non-GF receptor tyrosine kinase | *ABL-BCR* | Translocation | CML, acute leukaemias |
| 4. | NUCLEAR TRANSCRIPTION FACTORS | | | |
| | *C-MYC* | MYC | Translocation | Burkitt's lymphoma |
| | *N-MYC* | *MYC* | Amplification | Neuroblastoma, small cell Ca lung |
| | *L-MYC* | *MYC* | Amplification | Small cell Ca lung |
| 5. | CELL CYCLE REGULATORY PROTEINS | | | |
| | Cyclins | *Cyclin D* | Translocation | Ca breast, liver, mantle cell lymphoma |
| | | *Cyclin E* | Overexpression | Ca breast |
| | CDKs | *CDK4* | Amplification | Glioblastoma, melanoma, sarcomas |

# RAS gene

- RAS protein is **signal transducing protein**

- Point mutation of RAS family genes is the single **most common abnormality of Proto-oncogenes** in human tumor.

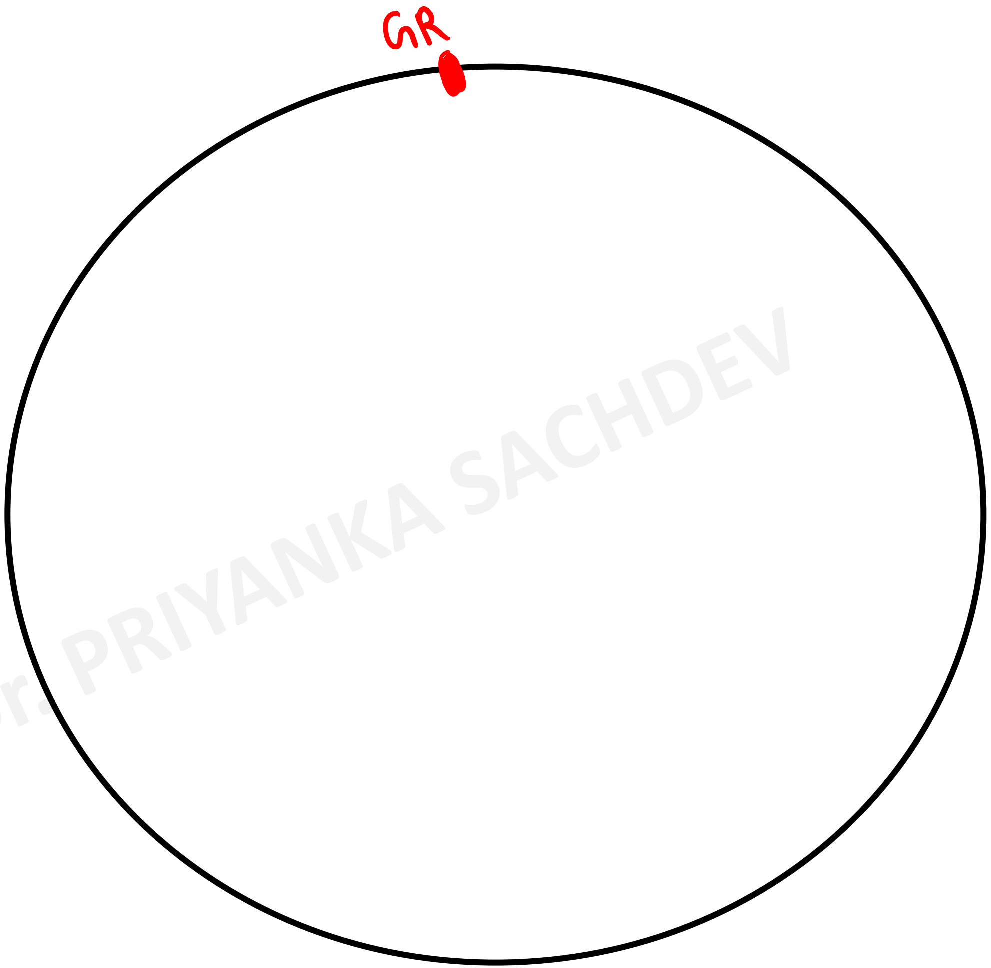
# 2 scenarios

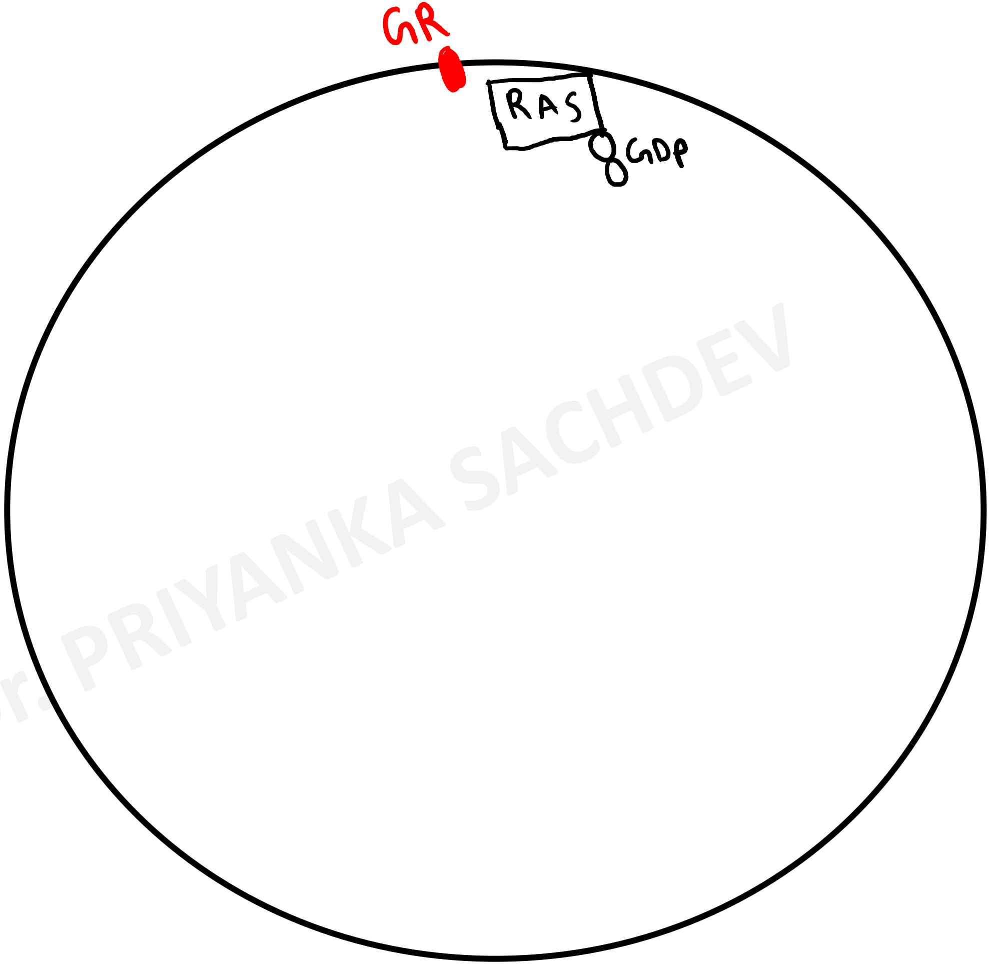
- Normally

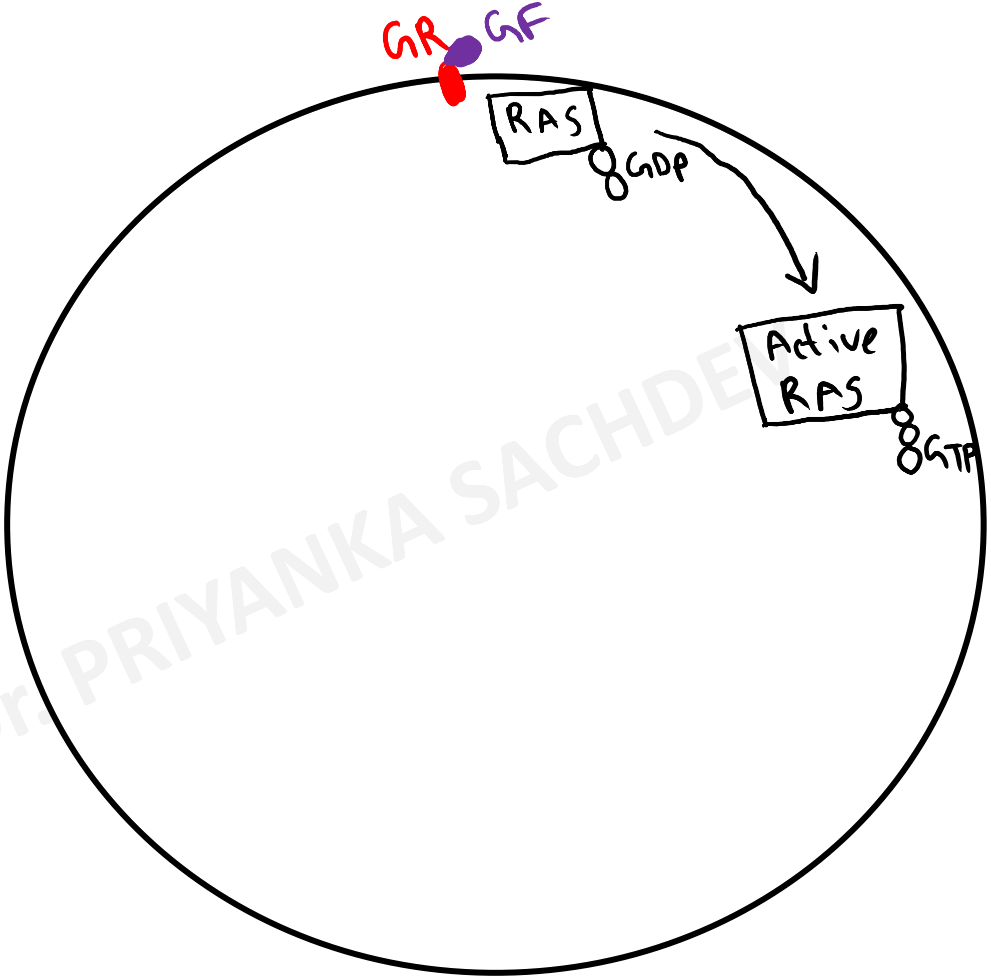
- Mutation

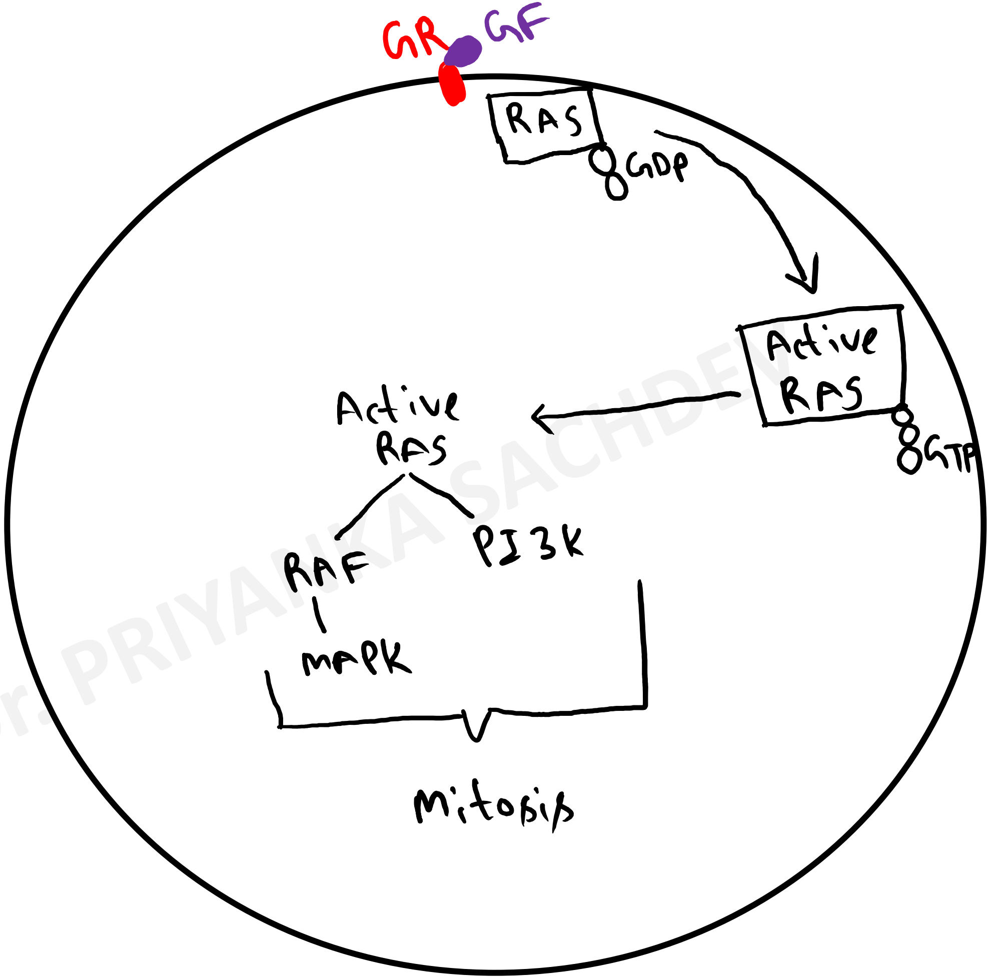
# NORMALLY

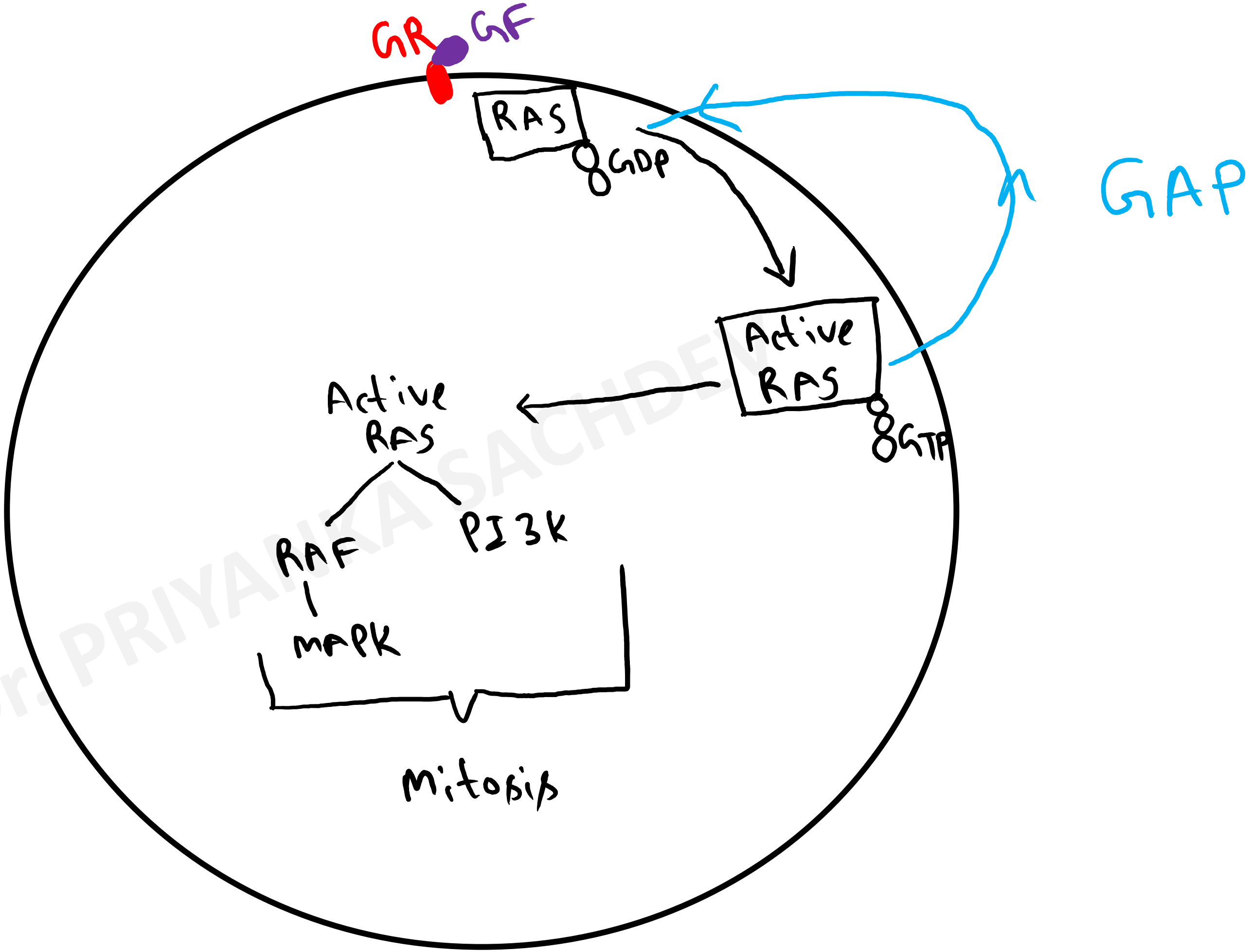
FOLLOW US

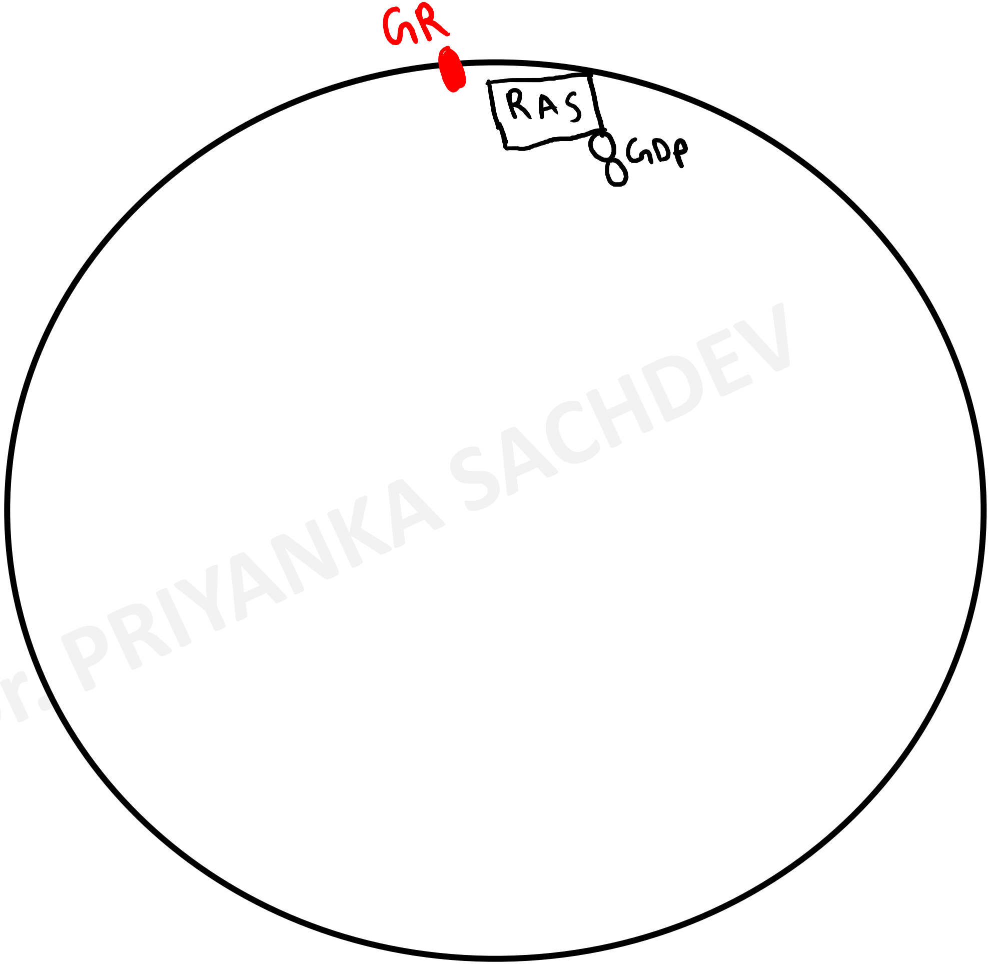

GR

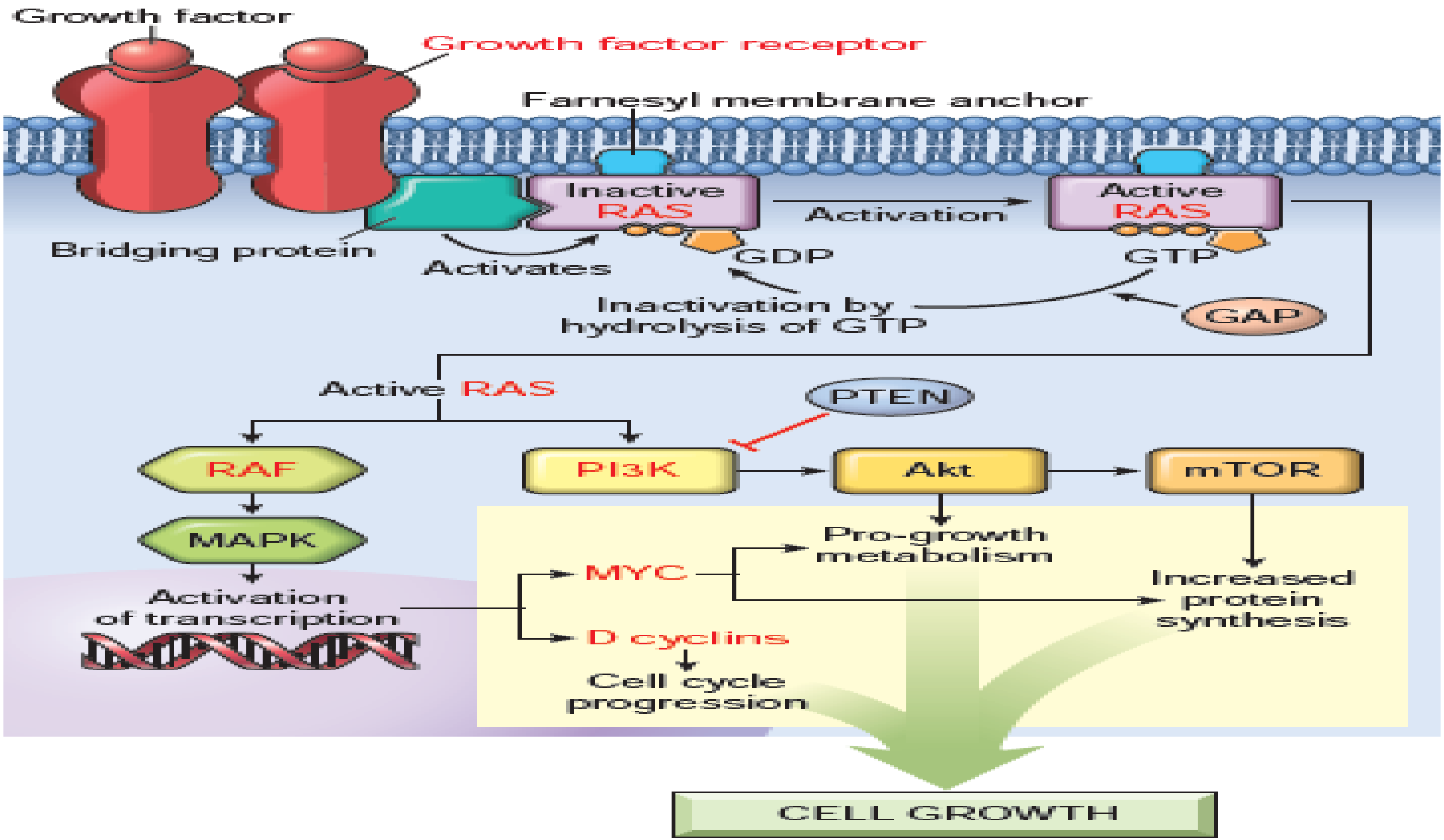

GR
RAS
GDP


GR
GF
RAS
GDP
Active RAS
GTP


GR
GF
RAS
GDP
Active RAS
GTP
Active RAS
RAF
PI3K
MAPK
Mitosis


GR
GF
RAS
GDP
Active RAS
GTP
GAP
Active RAS
RAF
PI3K
MAPK
Mitosis


GR
RAS
GDP


Growth factor
Growth factor receptor
Farnesyl membrane anchor
Inactive RAS
Activation
Active RAS
Bridging protein
Activates
GDP
GTP
Inactivation by hydrolysis of GTP
GAP
Active RAS
PTEN
RAF
PI3K
Akt
mTOR
MAPK
Pro-growth metabolism
MYC
Increased protein synthesis
Activation of transcription
D cyclins
Cell cycle progression
CELL GROWTH

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In Inactive state RAS proteins bind GDP

↓

Growth factors

↓

RAS proteins become activated by exchanging GDP for GTP

↓

Activated RAS recruits RAF-1 and also activates PI3K

↓

Mitosis

↓

GTPase Activating Proteins (GAP)

↓

GTP breaks into GDP

↓

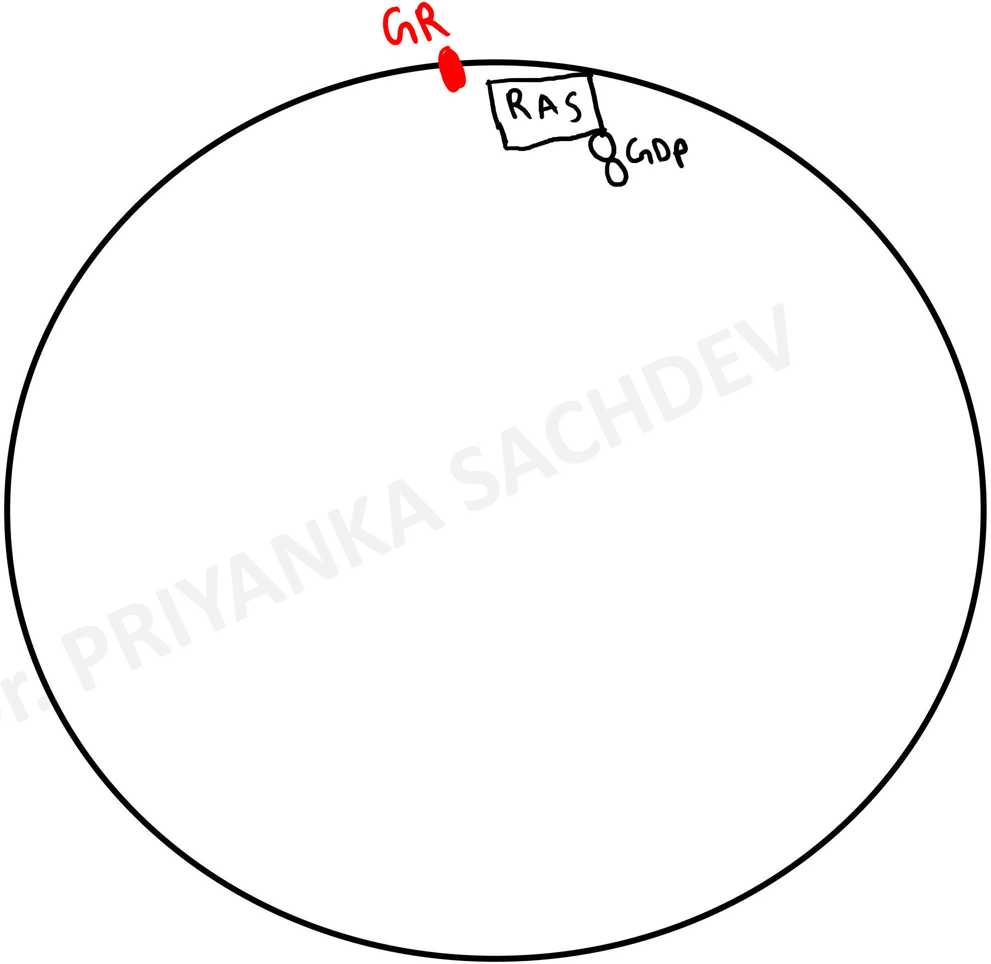
RAS Back to inactive state (Activated state is transient)

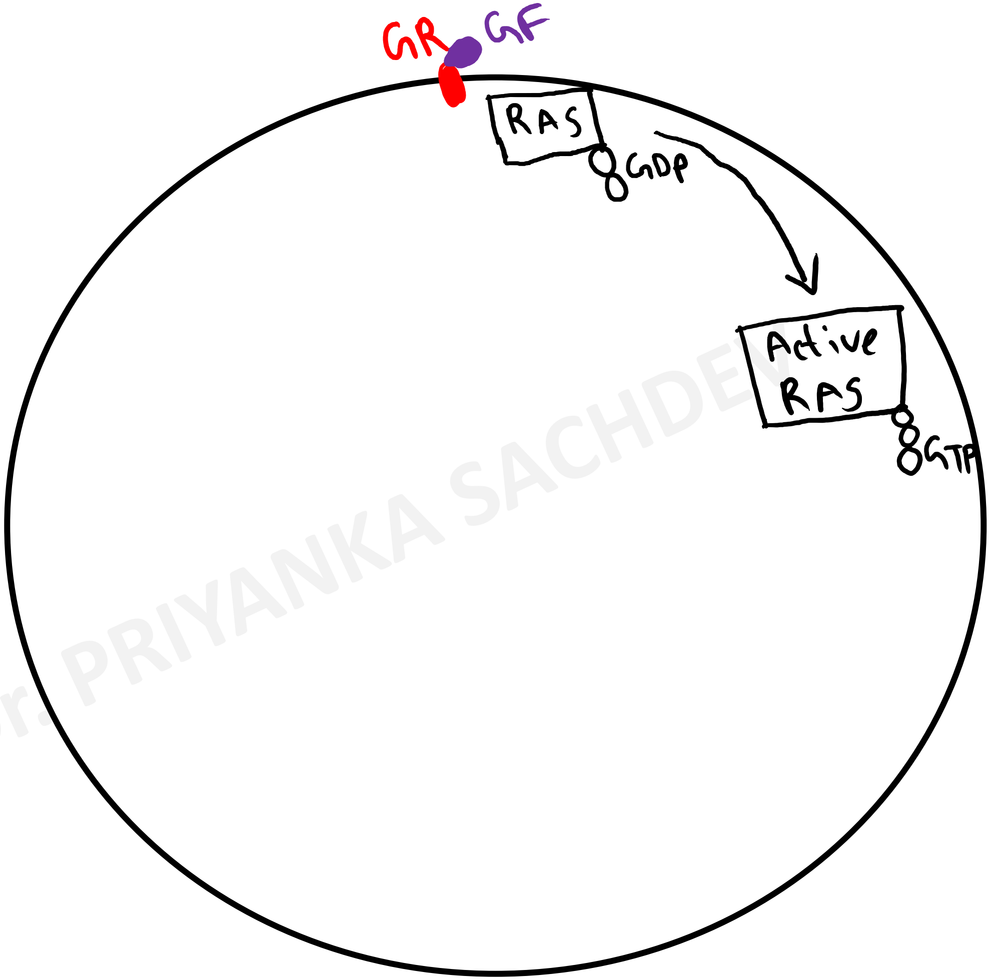
# 2 scenarios

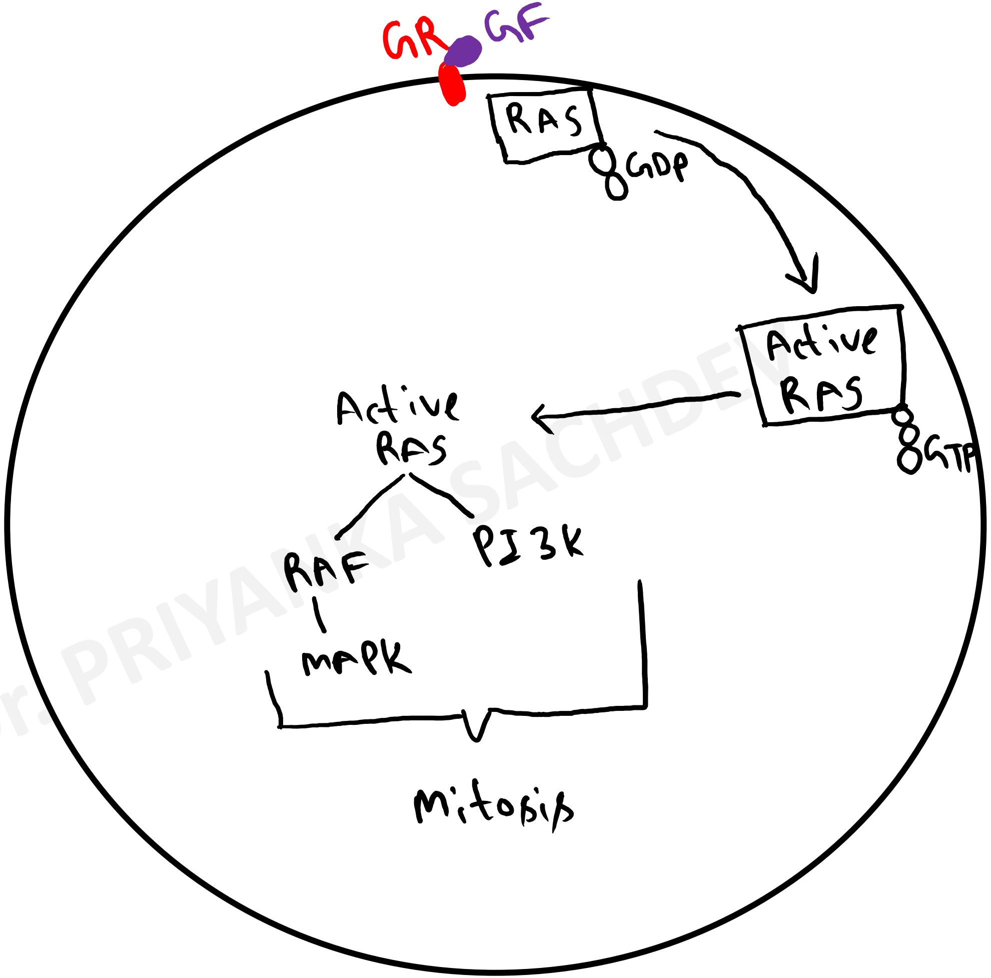
- Normally

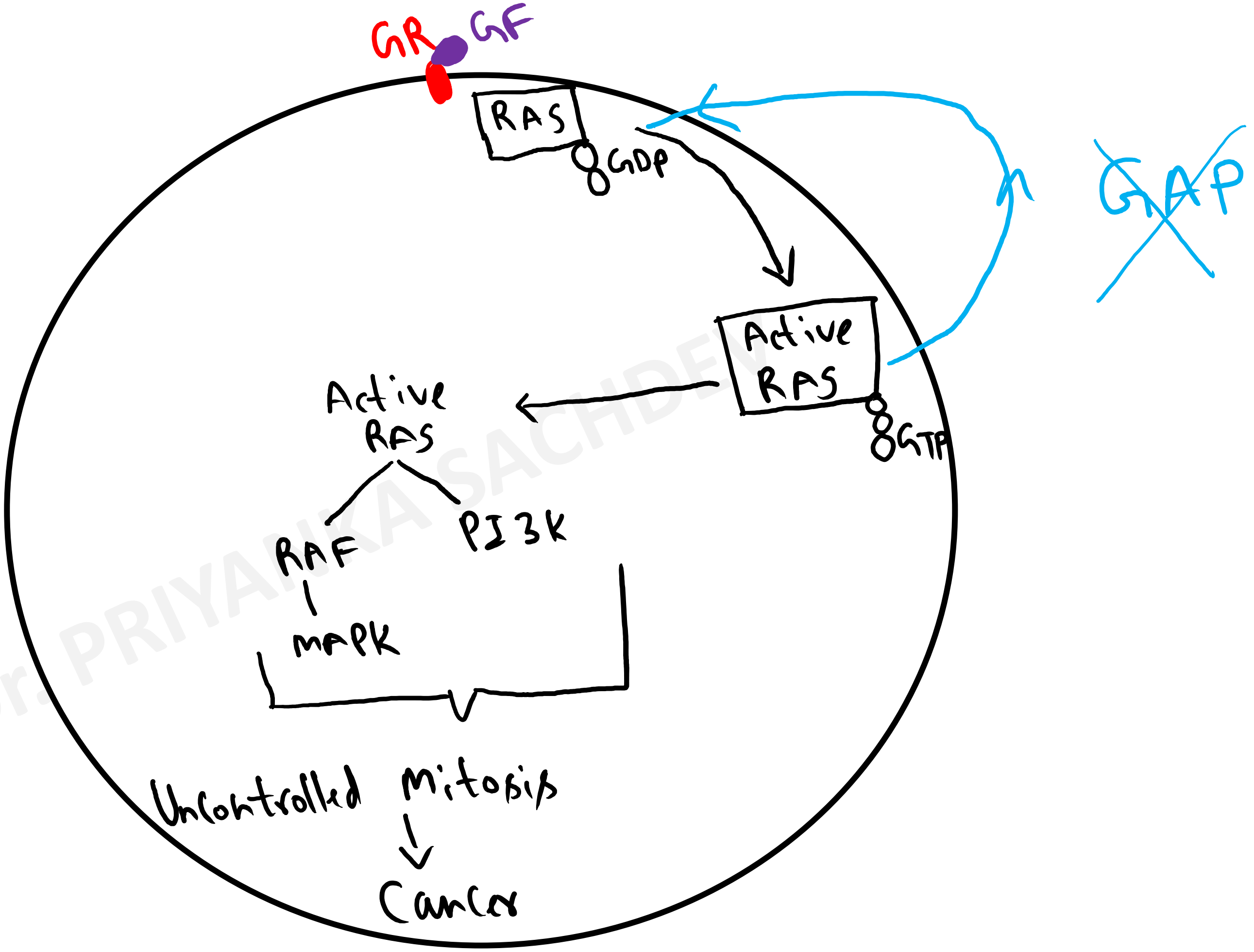
- Mutation

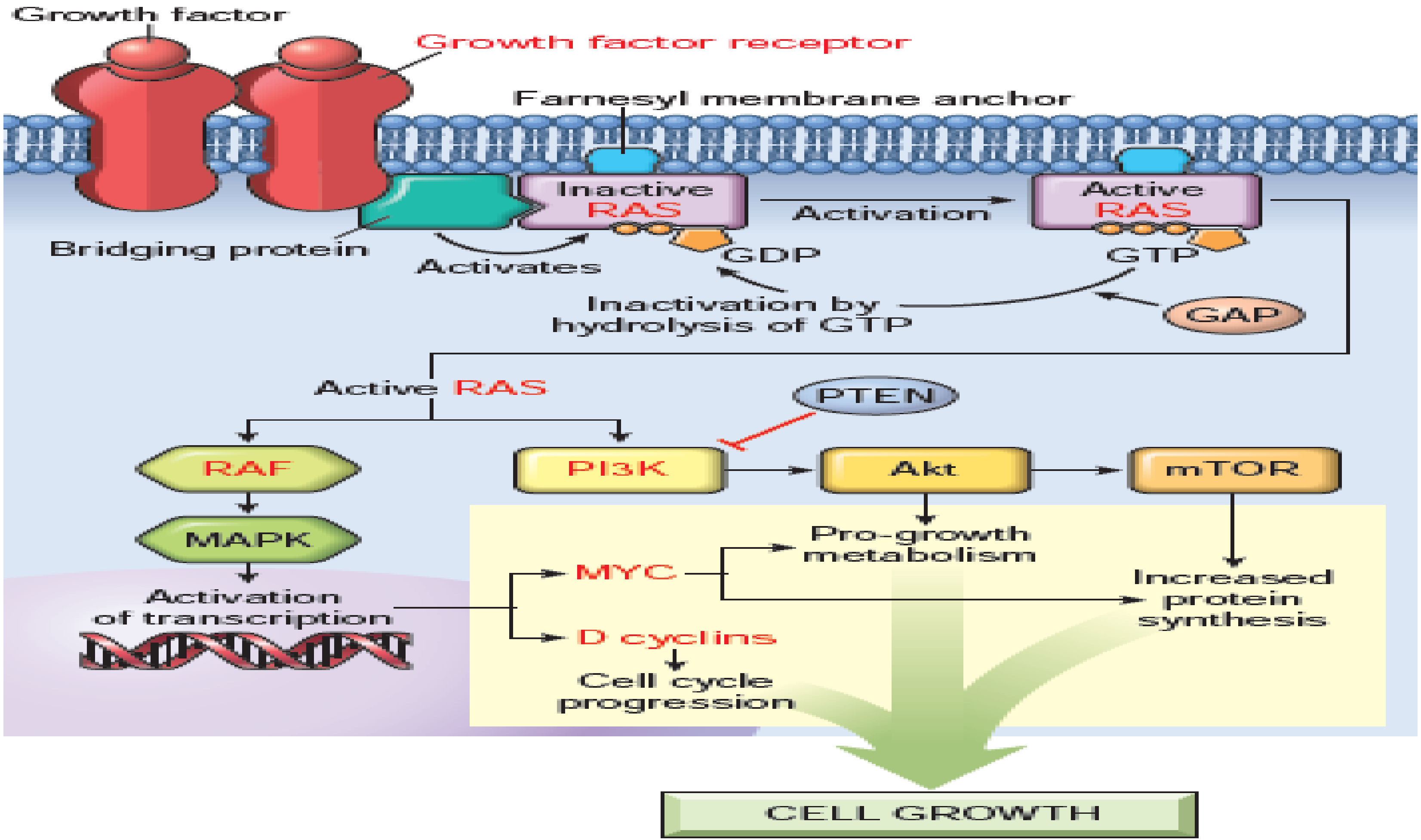
# MUTATION


GR
RAS
GDP


GR
GF
RAS
GDP
Active RAS
GTP


GR
GF
RAS
GDP
Active RAS
GTP
Active RAS
RAF
PI3K
MAPK
Mitosis


GR
GF
RAS
GDP
Active RAS
GTP
~~GAP~~
Active RAS
RAF
PI3K
MAPK
Uncontrolled Mitosis
Cancer



Growth factor

Growth factor receptor

Farnesyl membrane anchor

Bridging protein

Activates

Inactive RAS

GDP

Activation

Active RAS

GTP

Inactivation by hydrolysis of GTP

GAP

Active RAS

PTEN

RAF

MAPK

Activation of transcription

PI3K

Akt

mTOR

Pro-growth metabolism

MYC

Increased protein synthesis

D cyclins

Cell cycle progression

CELL GROWTH

**Mutation in the RAS gene**

↓

**GTPase Activating Proteins (GAP) not working**

↓

**GTPase acitivity cannot be increased**

↓

**No breakdown of GTP**

↓

**Permanent activation of RAS**

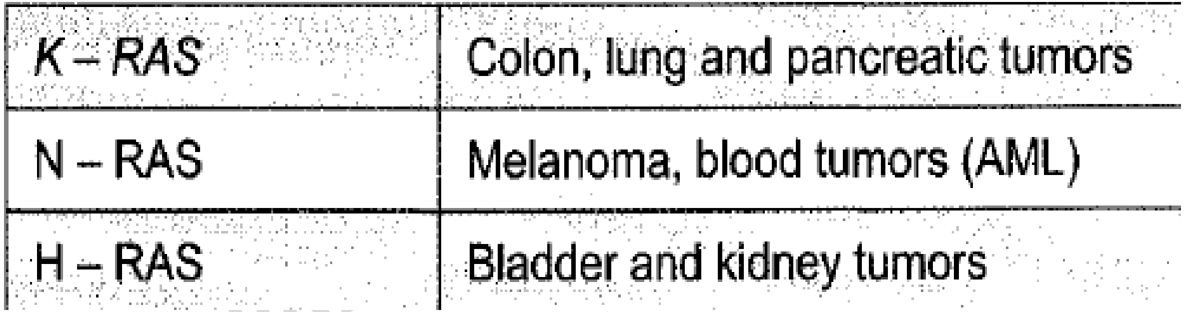
↓

**Uncontrolled mitosis**

↓

**Cancer**

# EXAMPLES



| | |
|---|---|
| *K – RAS* | Colon, lung and pancreatic tumors |
| N – RAS | Melanoma, blood tumors (AML) |
| H – RAS | Bladder and kidney tumors |

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# CLASSIFICATION

**5 classes→**

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- ii) Receptors of growth factors
- iii) Cytoplasmic signal transduction proteins
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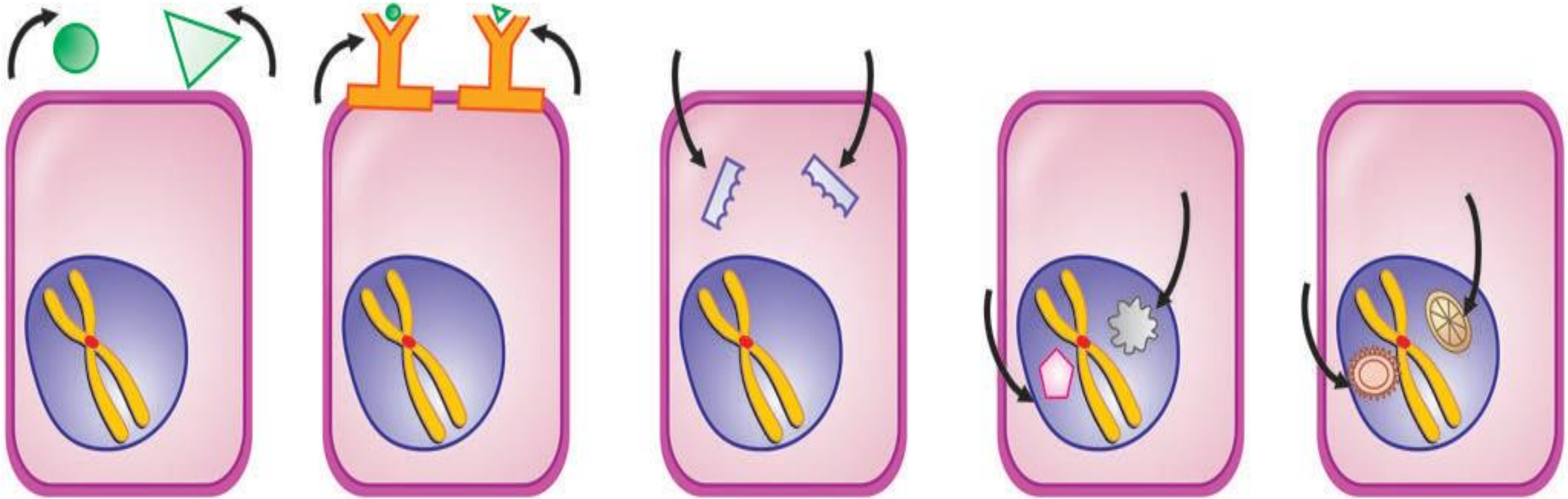
- v) Cell regulatory proteins



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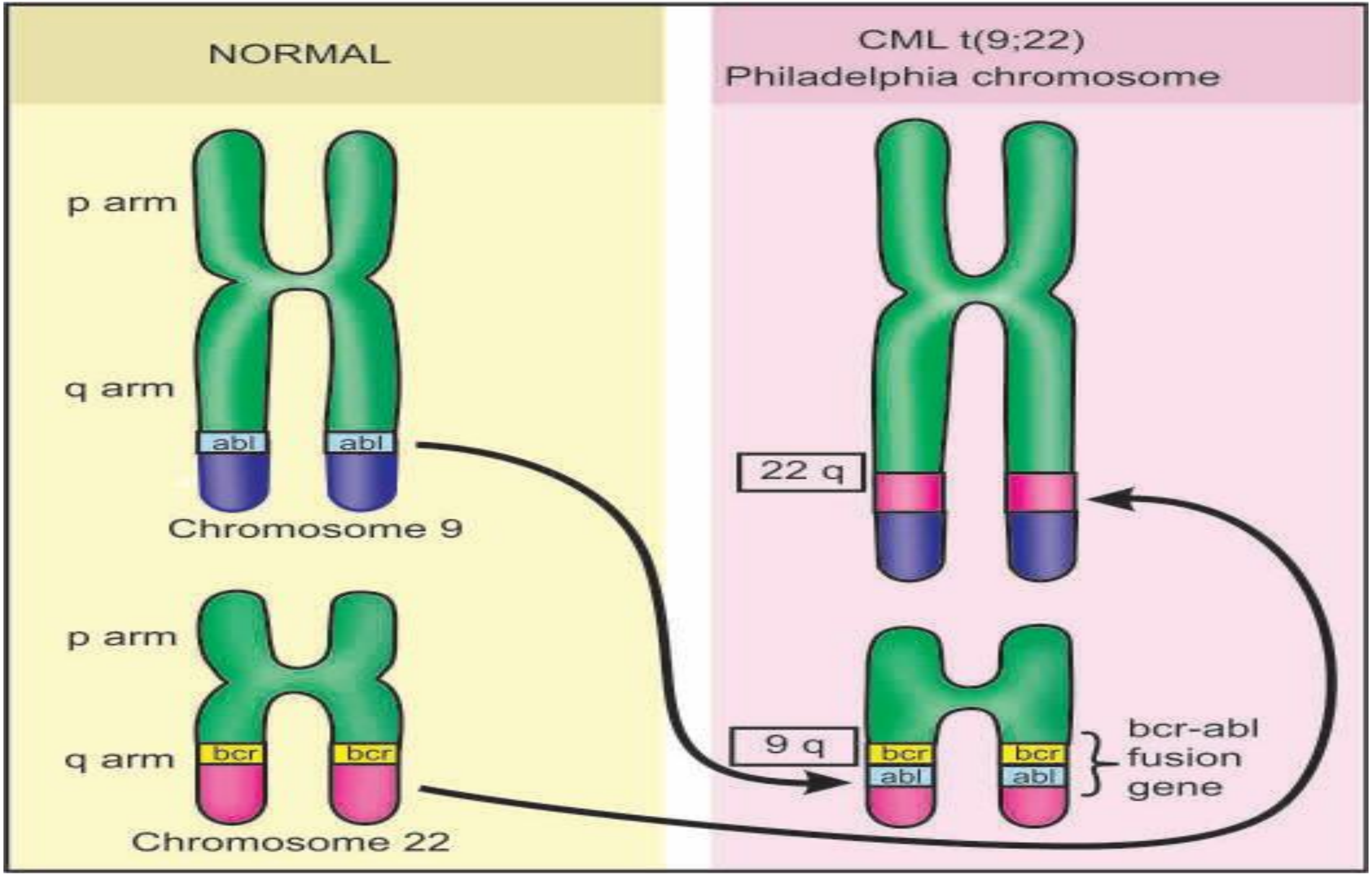
| iii) FGF | iii) RET-R | | iii) L-MYC | iii) CDK4 |
| iv) c-MET | iv) FMS-like | | | |

# ABL-BCR hybrid gene

- ABL gene is a protooncogene having tyrosine kinase activity.

# NORMALLY

- **ABL gene** → normal location on chromosome 9
- **BCR gene**→normal location on chromosome 22


NORMAL
CML t(9;22)
Philadelphia chromosome
p arm
q arm
abl
abl
Chromosome 9
p arm
q arm
bcr
bcr
Chromosome 22
22 q
9 q
bcr
bcr
abl
abl
bcr-abl fusion gene

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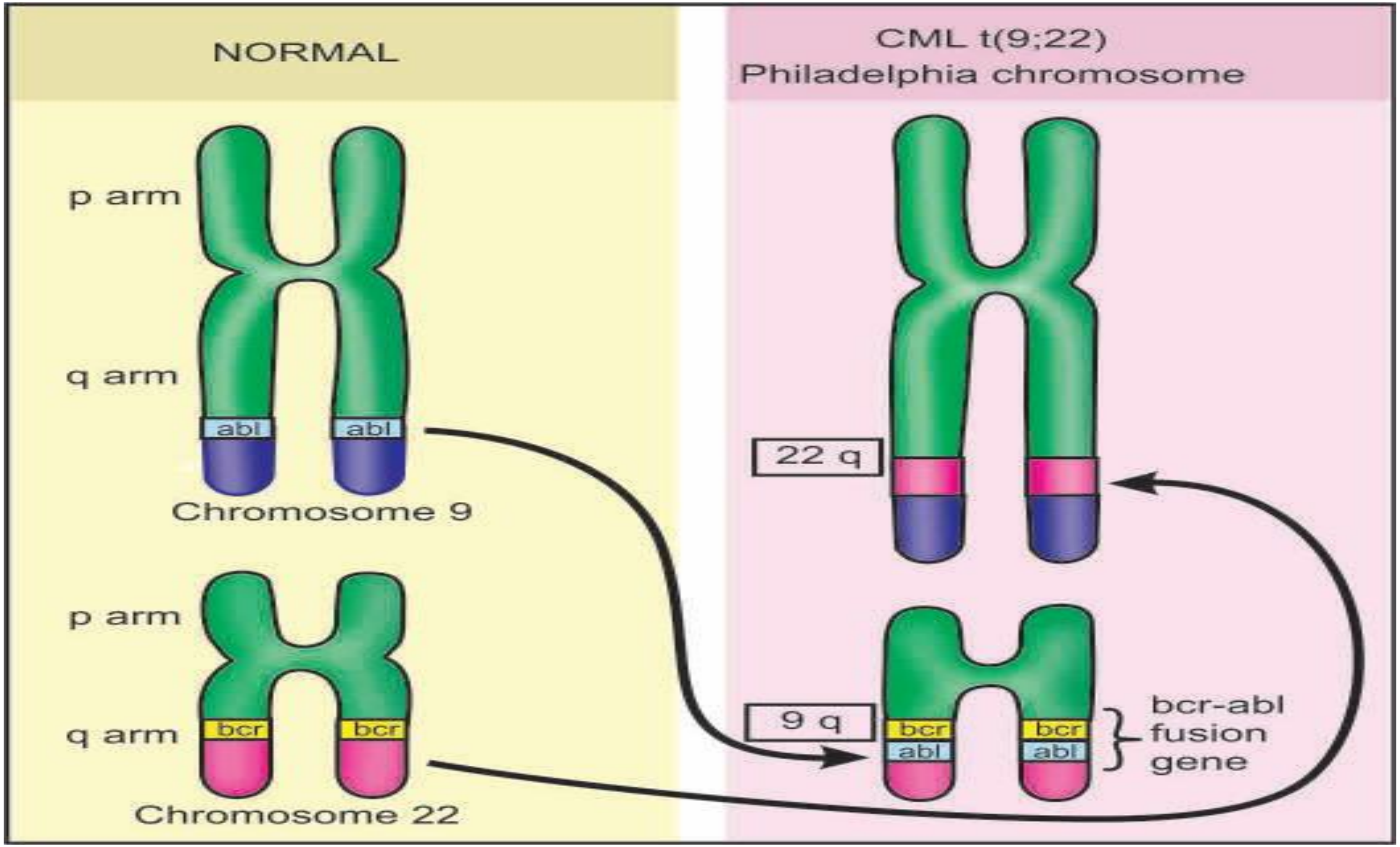
# IN TRANSLOCATION


NORMAL
CML t(9;22)
Philadelphia chromosome
p arm
q arm
abl
abl
Chromosome 9
22 q
p arm
q arm
bcr
bcr
Chromosome 22
9 q
bcr
abl
bcr
abl
bcr-abl fusion gene

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ABL gene → normal location on chromosome 9

↓

It is translocated to chromosome 22

↓

It fuses with BCR gene (breakpoint cluster region)

↓

Forms an ABL-BCR hybrid gene → Philadelphia chromosome on chromosome 22

↓

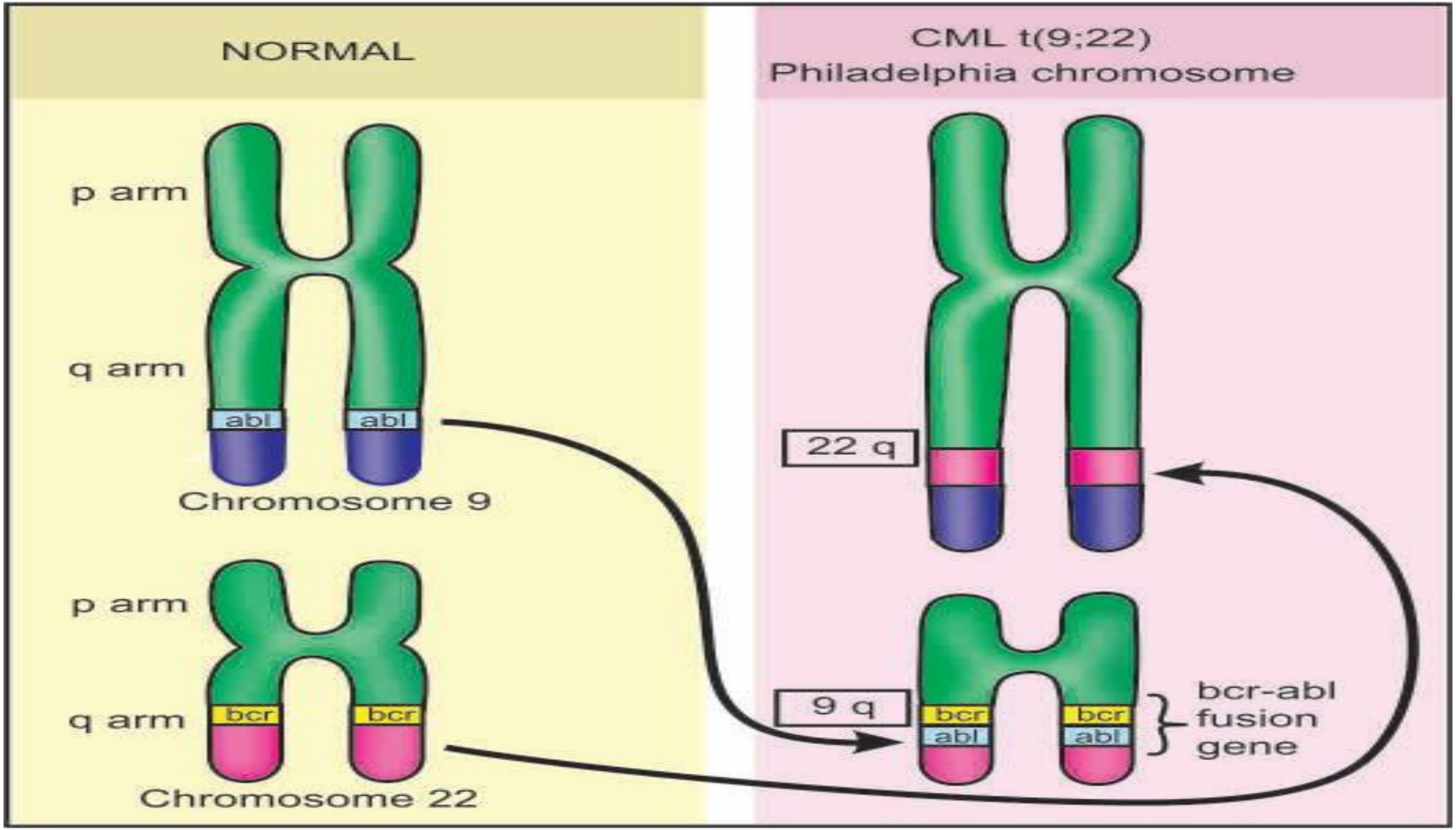
This hybrid do an abnormal signal transduction even without growth factors

↓

Uncontrolled mitosis

↓

Cancer


NORMAL
CML t(9;22)
Philadelphia chromosome
p arm
q arm
abl
abl
Chromosome 9
22 q
p arm
q arm
bcr
bcr
Chromosome 22
9 q
bcr
bcr
abl
abl
bcr-abl fusion gene

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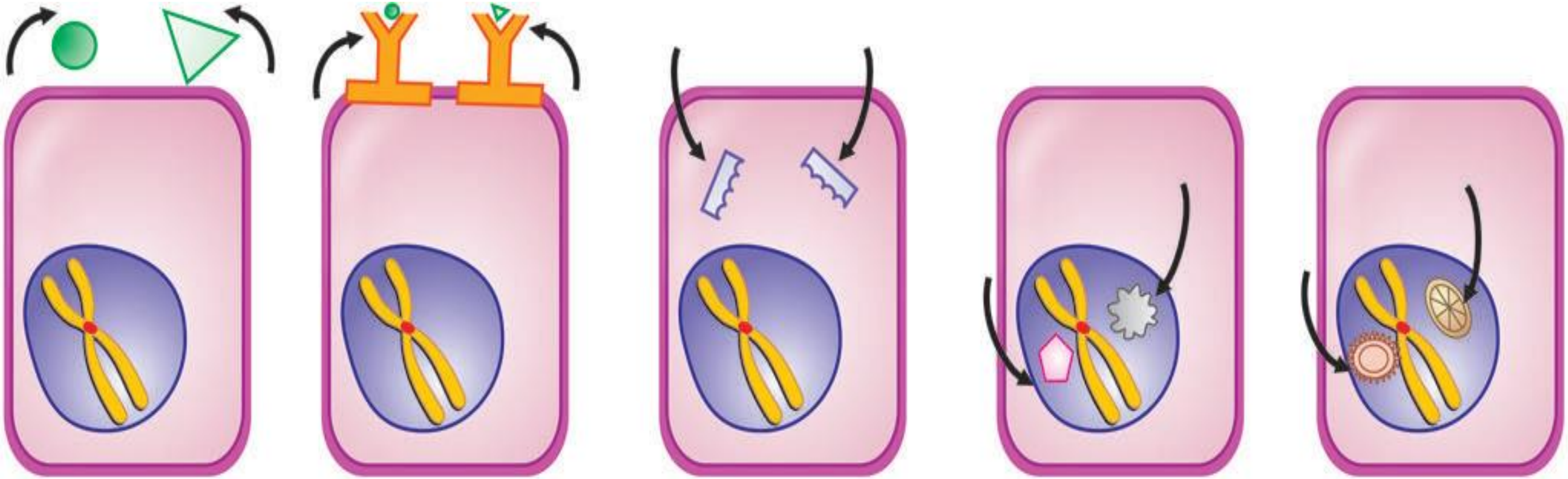
# EXAMPLE

- **CML**

- Now a days a specific tyosine kinase inhibitor drug called **imatinib** is used in treatment of CML
- This is an example of targeted drug therapy



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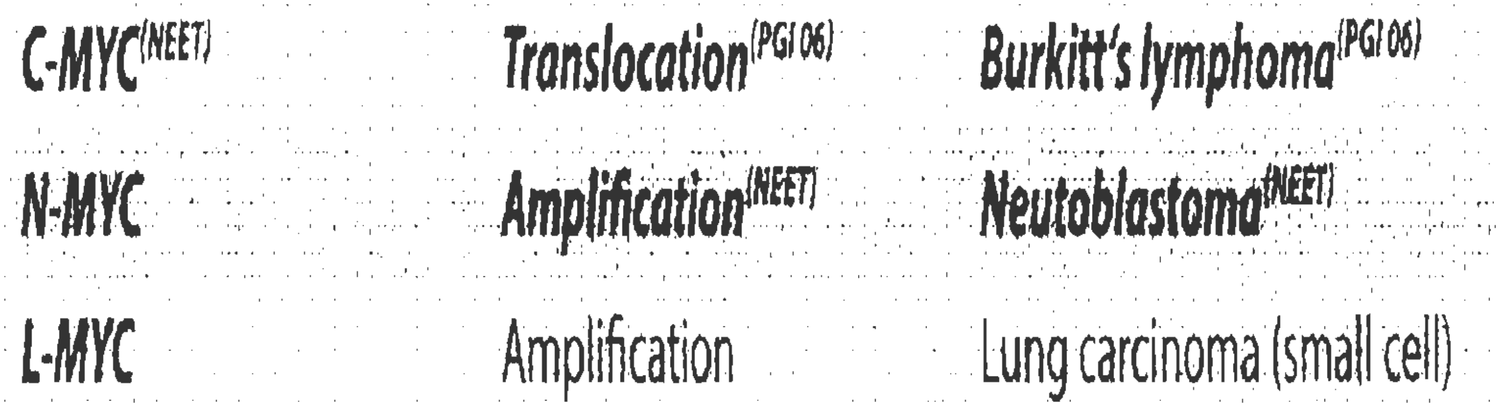
# MYC

- **MYC gene is a protooncogene having** nuclear regulatory activity (transcriptional activators).

- These are involved in carcinogenesis of many cancers



| | | |
|---|---|---|
| ***C-MYC*(NEET)** | ***Translocation*(PGI 06)** | ***Burkitt's lymphoma*(PGI 06)** |
| ***N-MYC*** | ***Amplification*(NEET)** | ***Neutoblastoma*(NEET)** |
| ***L-MYC*** | Amplification | Lung carcinoma (small cell) |

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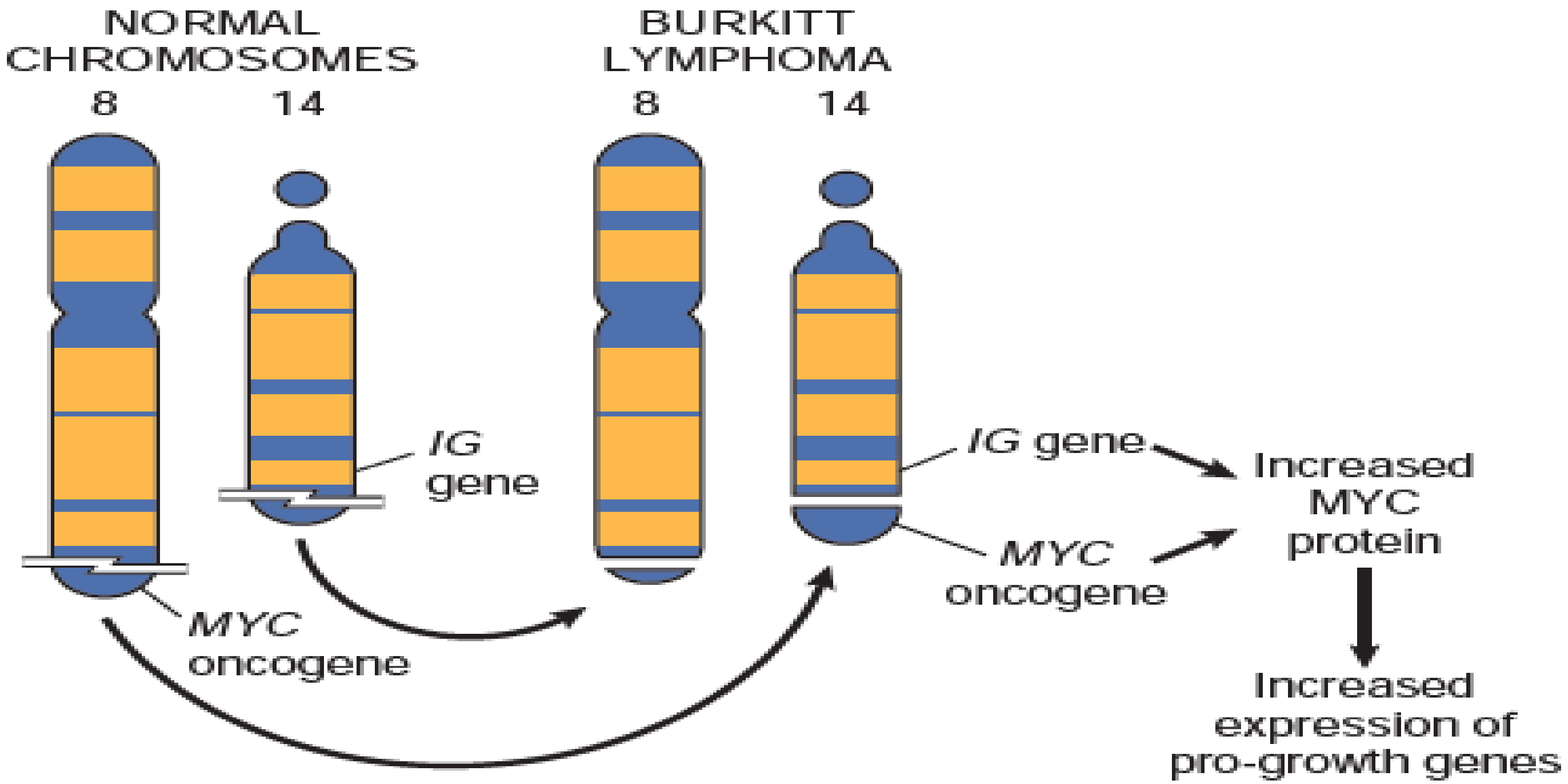
# NORMALLY

- MYC gene → normal location on chromosome 8
- IG gene→normal location on chromosome 14


NORMAL CHROMOSOMES
8
14
IG gene
MYC oncogene
BURKITT LYMPHOMA
8
14
IG gene
MYC oncogene
Increased MYC protein
Increased expression of pro-growth genes

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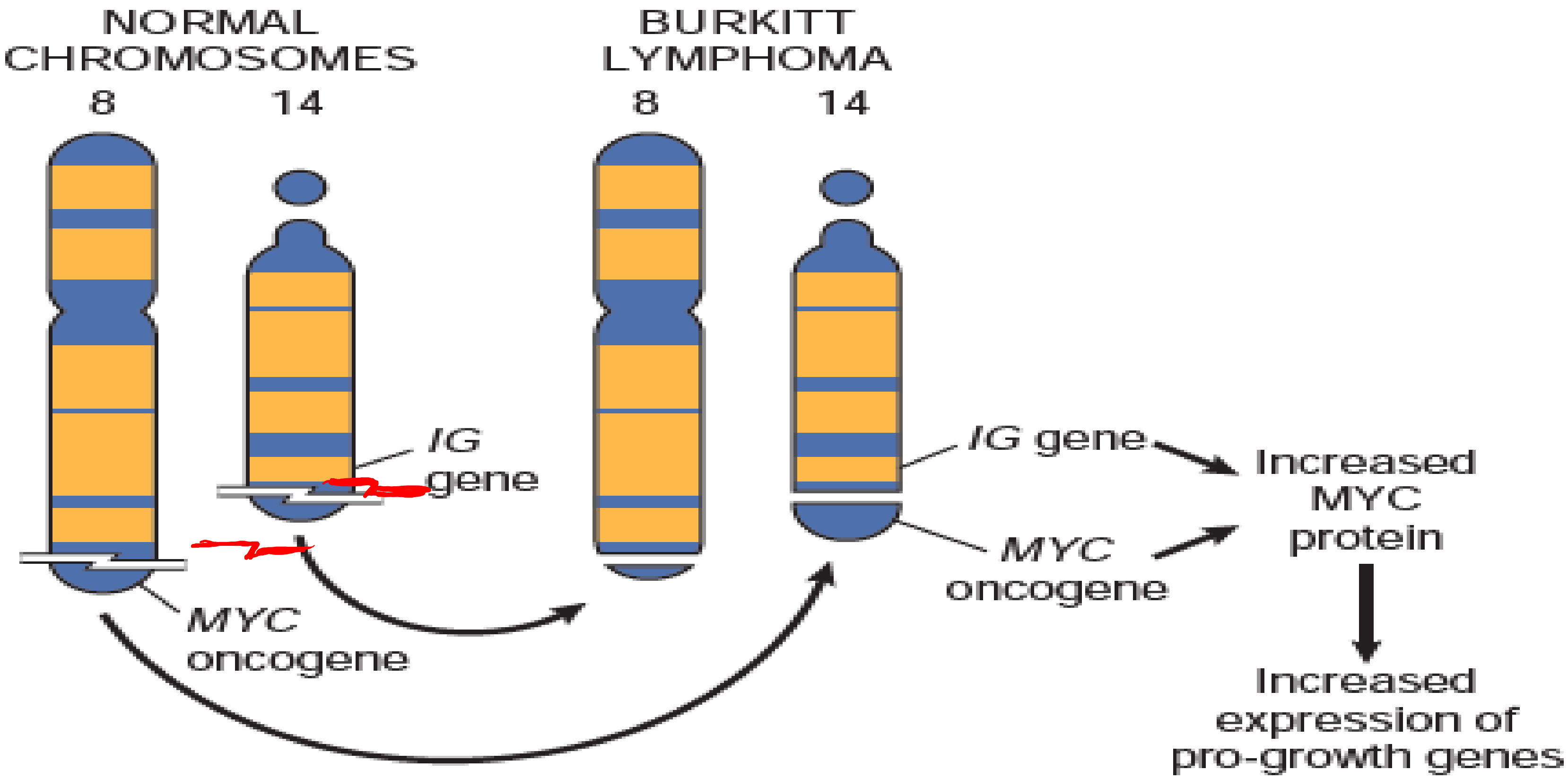
# IN TRANSLOCATION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8
14
IG gene
MYC oncogene
BURKITT LYMPHOMA
8
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IG gene
MYC oncogene
Increased MYC protein
Increased expression of pro-growth genes

**MYC gene → normal location on chromosome 8**

↓

**It is translocated to chromosome 14**

↓

**It fuses with IG gene**

↓

**Forms an MYC-IG hybrid gene**

↓

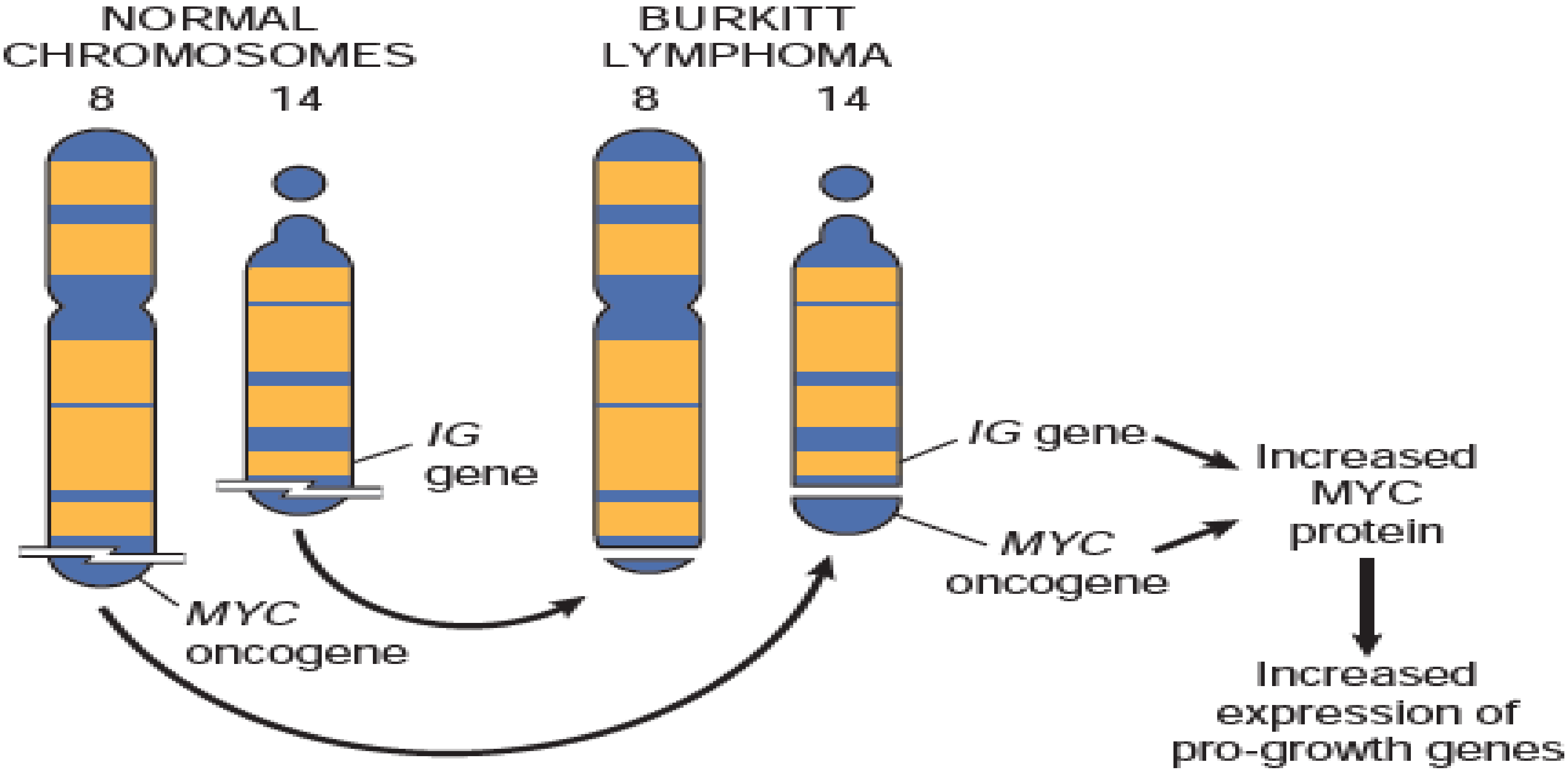
**This hybrid has abnormal** nuclear regulatory activity

↓

**Uncontrolled mitosis**

↓

**Cancer**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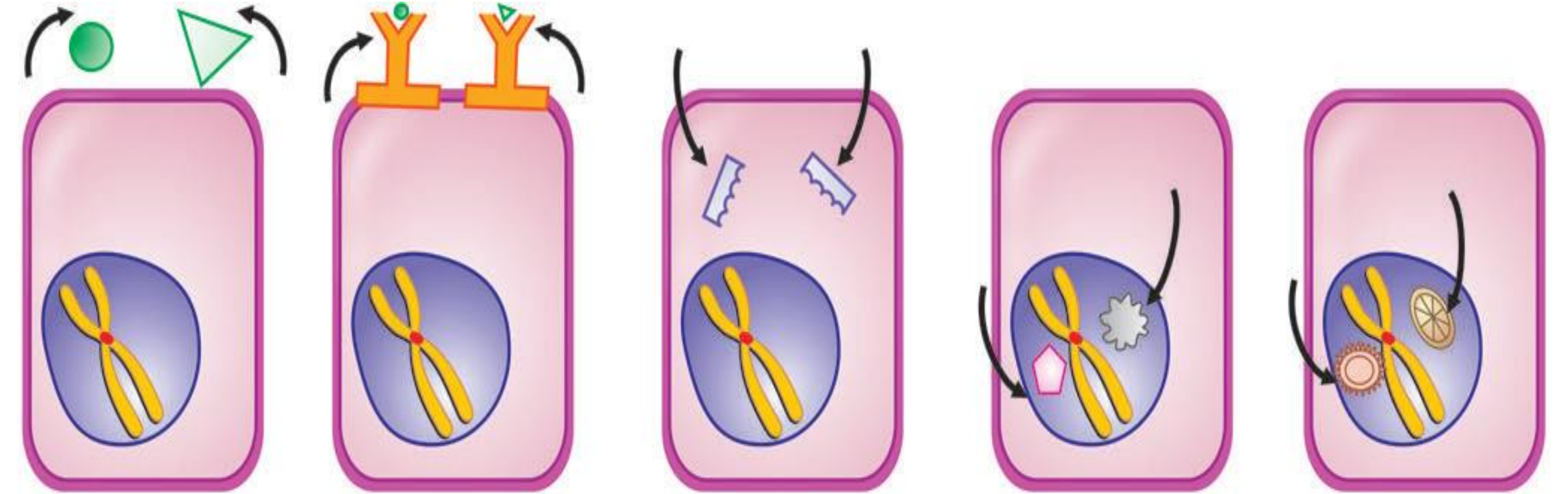

| GROWTH FACTORS | RECEPTORS FOR GFs | CYTOPLASMIC SIGNAL TRANSDUCTION PROTEINS | NUCLEAR TRANSCRIPTION FACTORS | CELL CYCLE REGULATORY PROTEINS |
|---|---|---|---|---|
| i) PDGF-β<br>ii) TGF-α<br>iii) FGF<br>iv) c-MET | i) EGF-R<br>ii) c-KIT -R<br>iii) RET-R<br>iv) FMS-like | I) Mutated RAS<br>ii) ABL-BCR | i) C-MYC<br>ii) N-MYC<br>iii) L-MYC | i) Cyclin D<br>ii) Cyclin E<br>iii) CDK4 |

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# POLLS 1

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Neoplasia E02

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**The best example of a proto-oncogene activated by point mutation is -**

a) Ras
b) N-myc
c) L-myc
d) Abl

Dr.

# A

**Philadelphia chromosome is an example of-**

a) Balanced translocation
b) Deletion
c) Non-dysjunction
d) Duplication

Dr. PRI

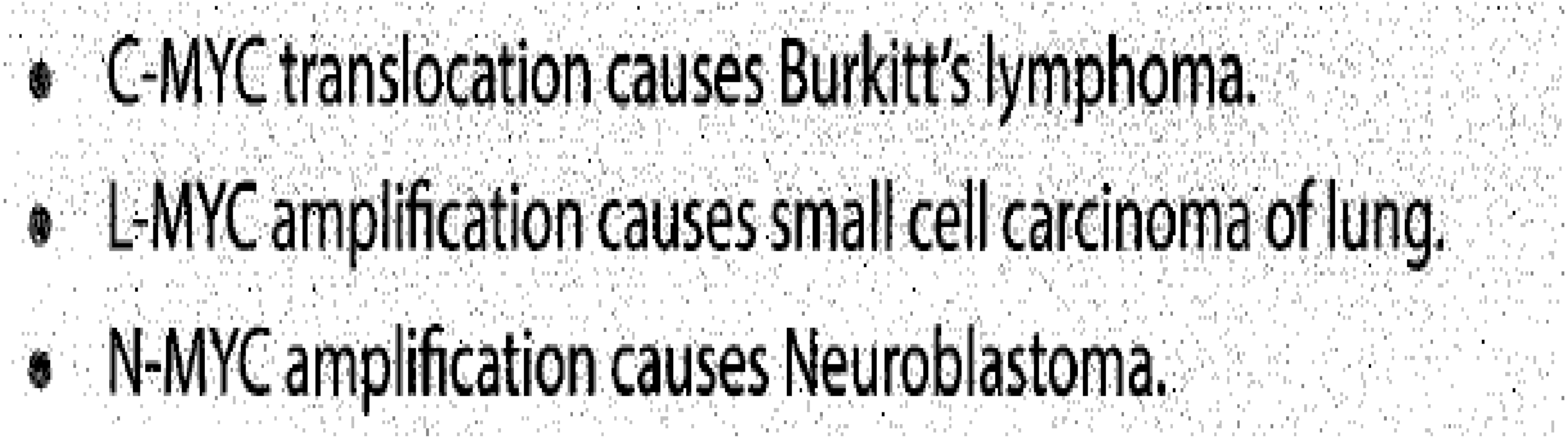
# A

**Amplification of N myc is associated with which tumour ?**

a) Neuroblastoma
b) Retinoblastoma
c) Osteosarcoma
d) Neuroma

Dr. Pr

# A

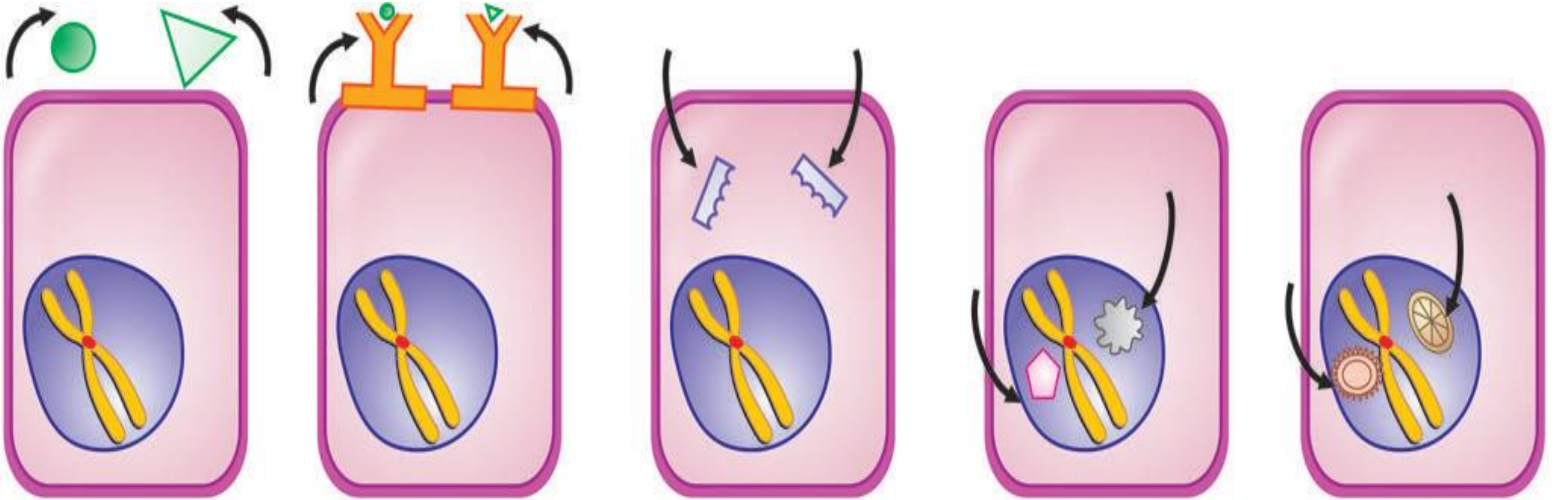


- C-MYC translocation causes Burkitt's lymphoma.
- L-MYC amplification causes small cell carcinoma of lung.
- N-MYC amplification causes Neuroblastoma.

# All are growth promoting oncogenes except -

- a) F GF
- b) TGF-a
- c) TGF-B
- d) PDGF

# c



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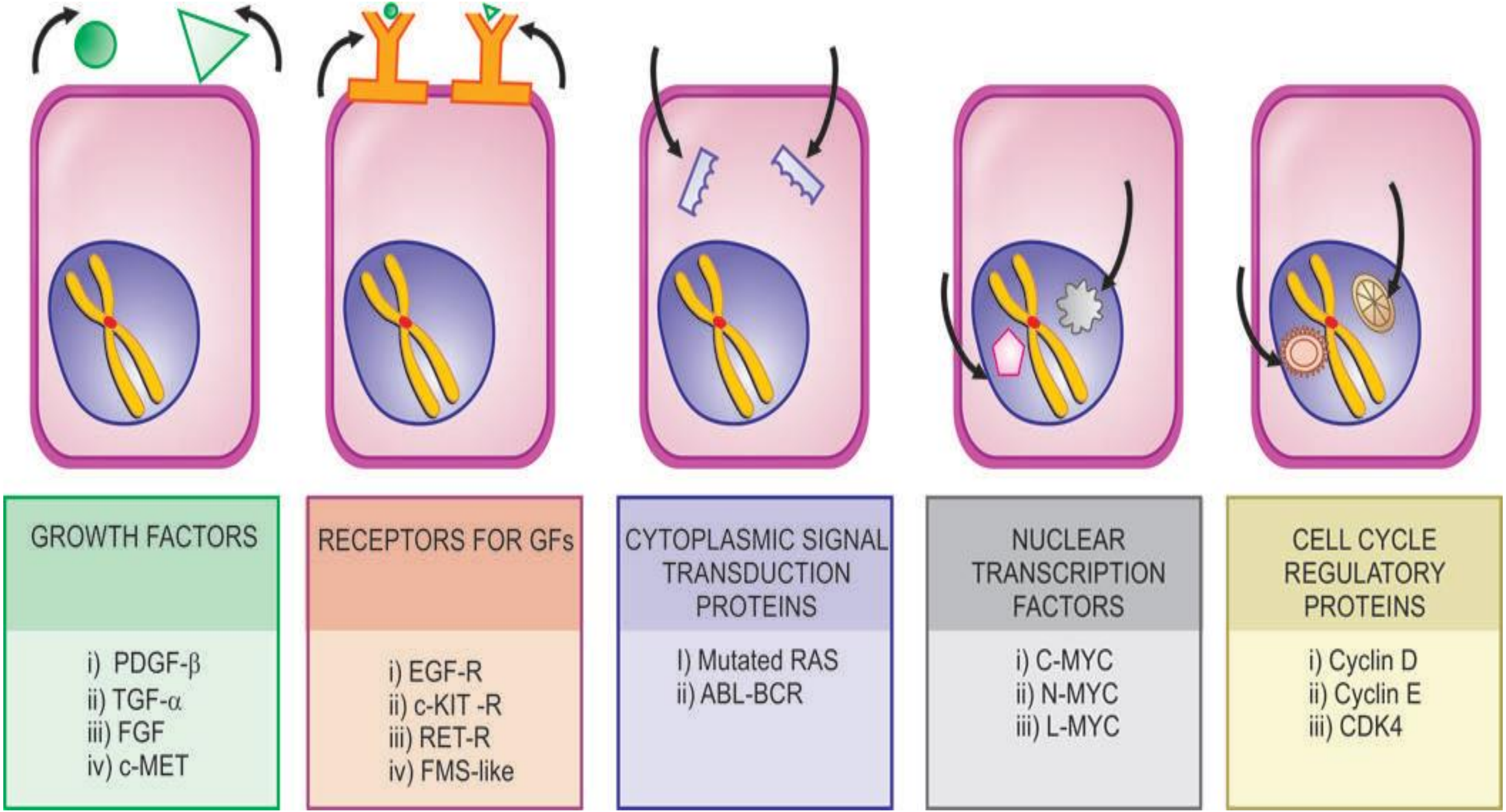
# MYC gene is -

- a) **Protein kinase inhibitor**
- **b) Growth factor inhibitor**
- **c) GTPase**
- **d) Transcription activator**

# D



**GROWTH FACTORS**

i) PDGF-β
ii) TGF-α
iii) FGF
iv) c-MET

**RECEPTORS FOR GFs**

i) EGF-R
ii) c-KIT -R
iii) RET-R
iv) FMS-like

**CYTOPLASMIC SIGNAL TRANSDUCTION PROTEINS**

I) Mutated RAS
ii) ABL-BCR

**NUCLEAR TRANSCRIPTION FACTORS**

i) C-MYC
ii) N-MYC
iii) L-MYC

**CELL CYCLE REGULATORY PROTEINS**

i) Cyclin D
ii) Cyclin E
iii) CDK4

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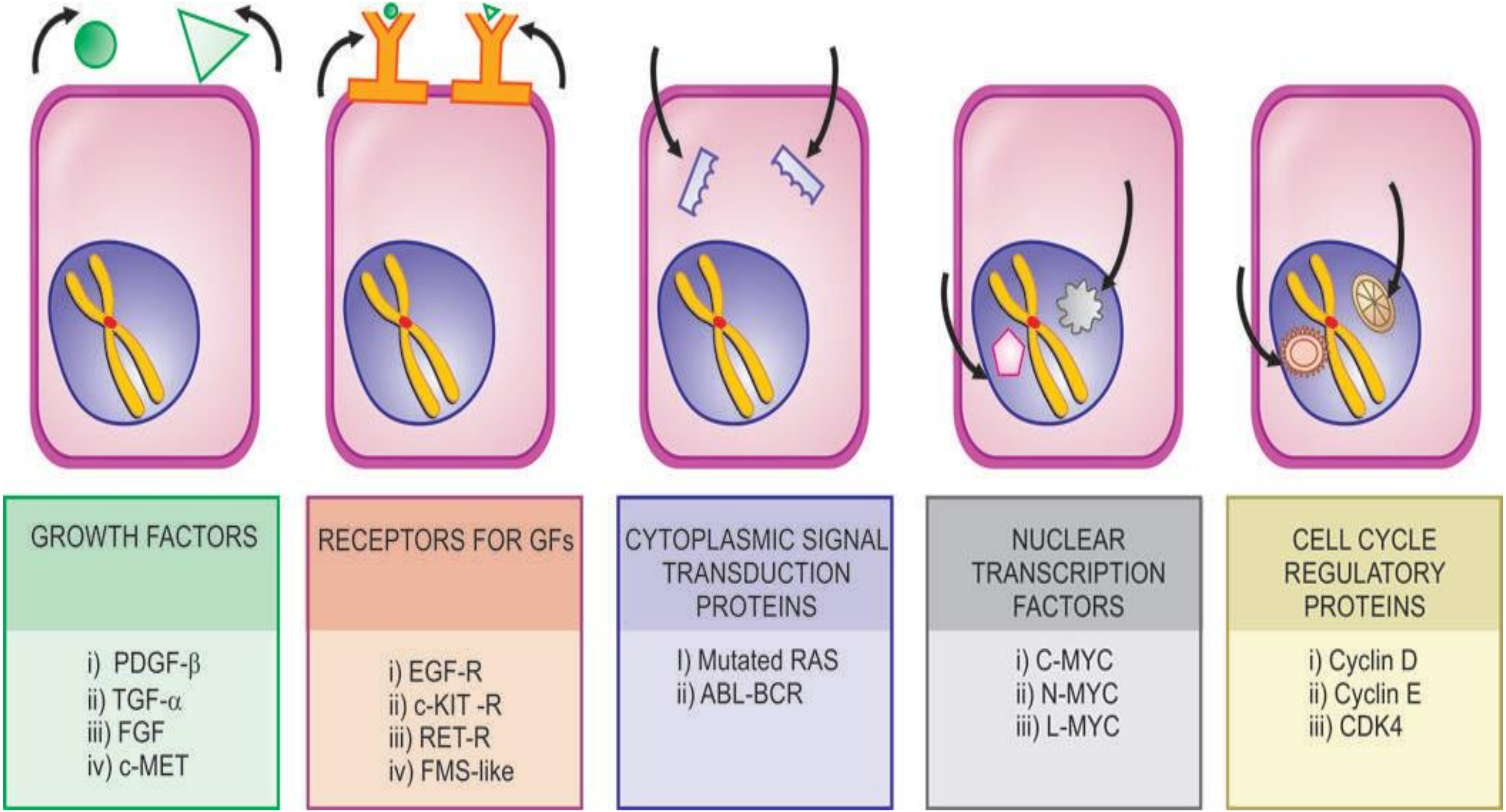
# Which of the following has tumor promoting effect?

- a) BRAC
- b) RB
- c) MYC
- d) p16

# c



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# In the MAPK pathway, the activation of RAS is counteracted by

a) Protein kinase C

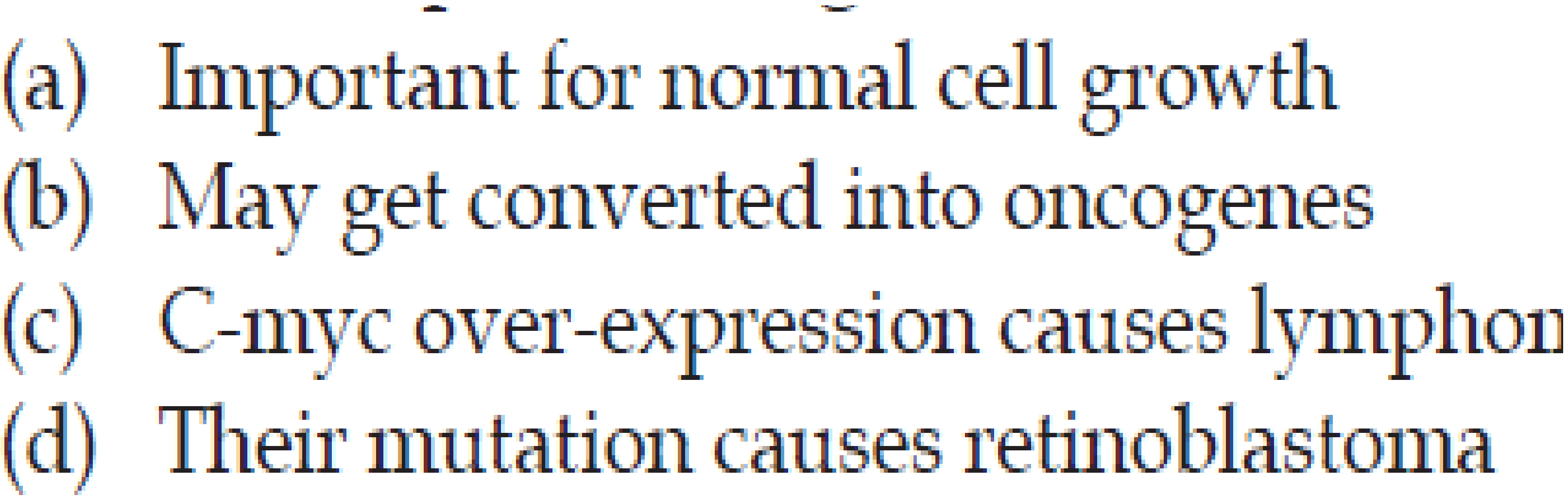
b) GTPase activating protein

c) Phosphatidyl inositol

d) Inositol triphosphate

# B

# False about proto oncogenes



(a) Important for normal cell growth

(b) May get converted into oncogenes

(c) C-myc over-expression causes lympho

(d) Their mutation causes retinoblastoma

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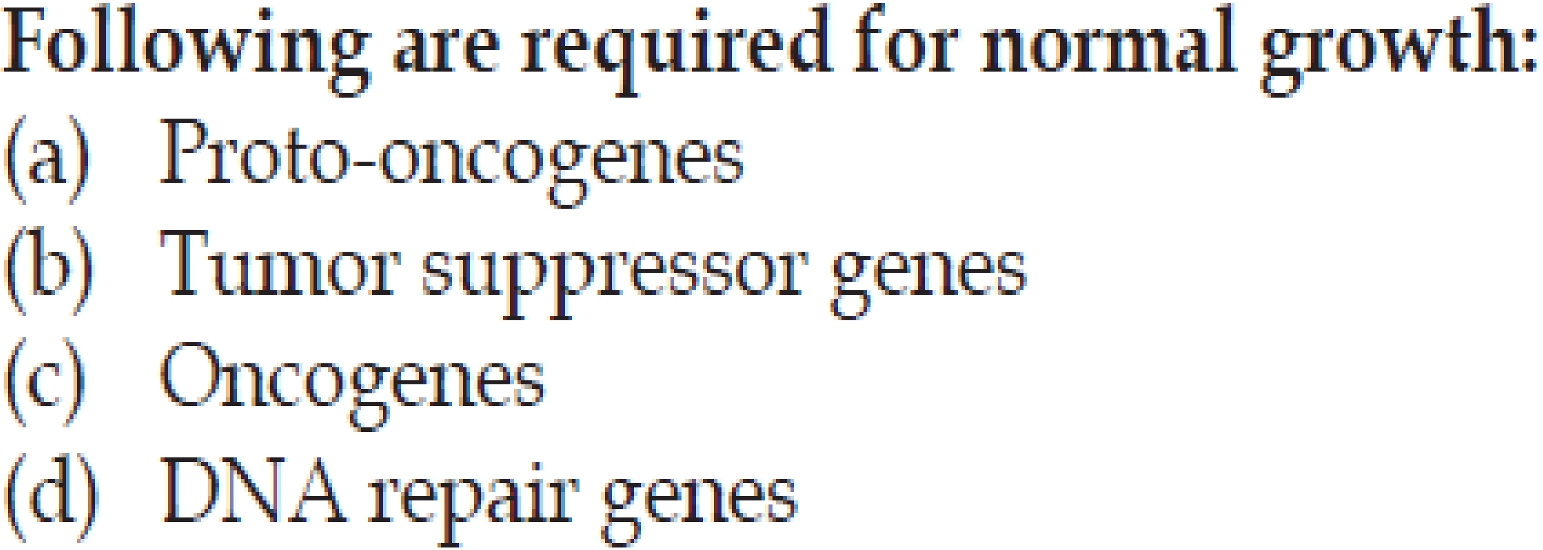
# D

# Following are required for normal growth exept



Following are required for normal growth:

(a) Proto-oncogenes
(b) Tumor suppressor genes
(c) Oncogenes
(d) DNA repair genes

# c

Growth factor oncogene is:

(a) Myc
(b) Fos
(c) Sis
(d) Jun

Dr. PRIYA

# c

|  | TYPE | PROTO-ONCOGENE | MECHANISM | ASSOCIATED HUMAN TUMOURS |
|---|---|---|---|---|
| 1. | GROWTH FACTORS |  |  |  |
|  | i) *PDGF-β* | *SIS* | Overexpression | Gliomas, sarcoma |
|  | ii) *TGF-α* | *RAS* | Overexpression | Carcinomas, astrocytoma |
|  | iii) *FGF* | *HST-1*<br>INT-2 | Overexpression<br>Amplification | Bowel cancers<br>Breast cancer |
|  | iv) *c-MET* | HGF | Overexpression | Follicular carcinoma thyroid |
| 2. | RECEPTORS FOR GROWTH FACTORS |  |  |  |
|  | i) *EGF* receptors | *ERB B1(HER 1)*<br>ERB B2 (*HER 2/neu)* | Overexpression<br>Amplification | Squamous cell carcinoma lung, glioblastoma<br>Ca breast, ovary, stomach, lungs |
|  | ii) *c-KIT* receptor (Steel factor) | c-KIT | Point mutation | GIST |
|  | iii) RET receptor | RET | Point mutation | MEN type 2A and type 2B, medullary ca thyroid |
|  | iv) FMS-like tyrosine kinase receptor | FLT-3 gene | Point mutation | Acute myeloid leukaemia |
| 3. | CYTOPLASMIC SIGNAL TRANSDUCTION PROTEINS |  |  |  |
|  | GTP-bound | *RAS* | Point mutation | Common in 1/3rd human tumours, Ca lung, colon, pancreas |
|  | Non-GF receptor tyrosine kinase | *ABL-BCR* | Translocation | CML, acute leukaemias |
| 4. | NUCLEAR TRANSCRIPTION FACTORS |  |  |  |
|  | *C-MYC* | MYC | Translocation | Burkitt's lymphoma |
|  | *N-MYC* | *MYC* | Amplification | Neuroblastoma, small cell Ca lung |
|  | *L-MYC* | *MYC* | Amplification | Small cell Ca lung |
| 5. | CELL CYCLE REGULATORY PROTEINS |  |  |  |
|  | Cyclins | *Cyclin D*<br>*Cyclin E* | Translocation<br>Overexpression | Ca breast, liver, mantle cell lymphoma<br>Ca breast |
|  | CDKs | *CDK4* | Amplification | Glioblastoma, melanoma, sarcomas |

# In cancer

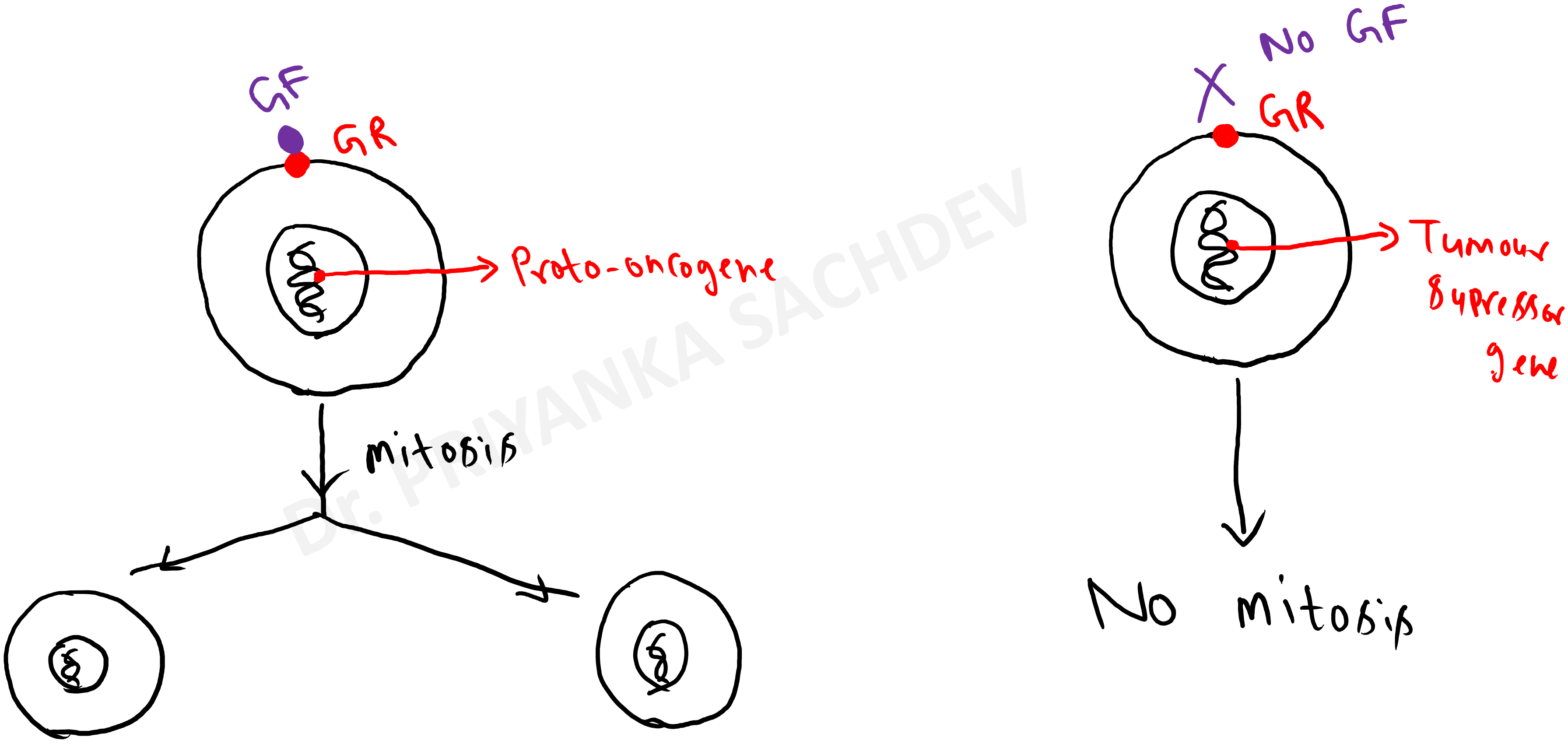
i) Overstimulation of proto-oncogenes

ii) Inhibition of tumour-suppressor genes

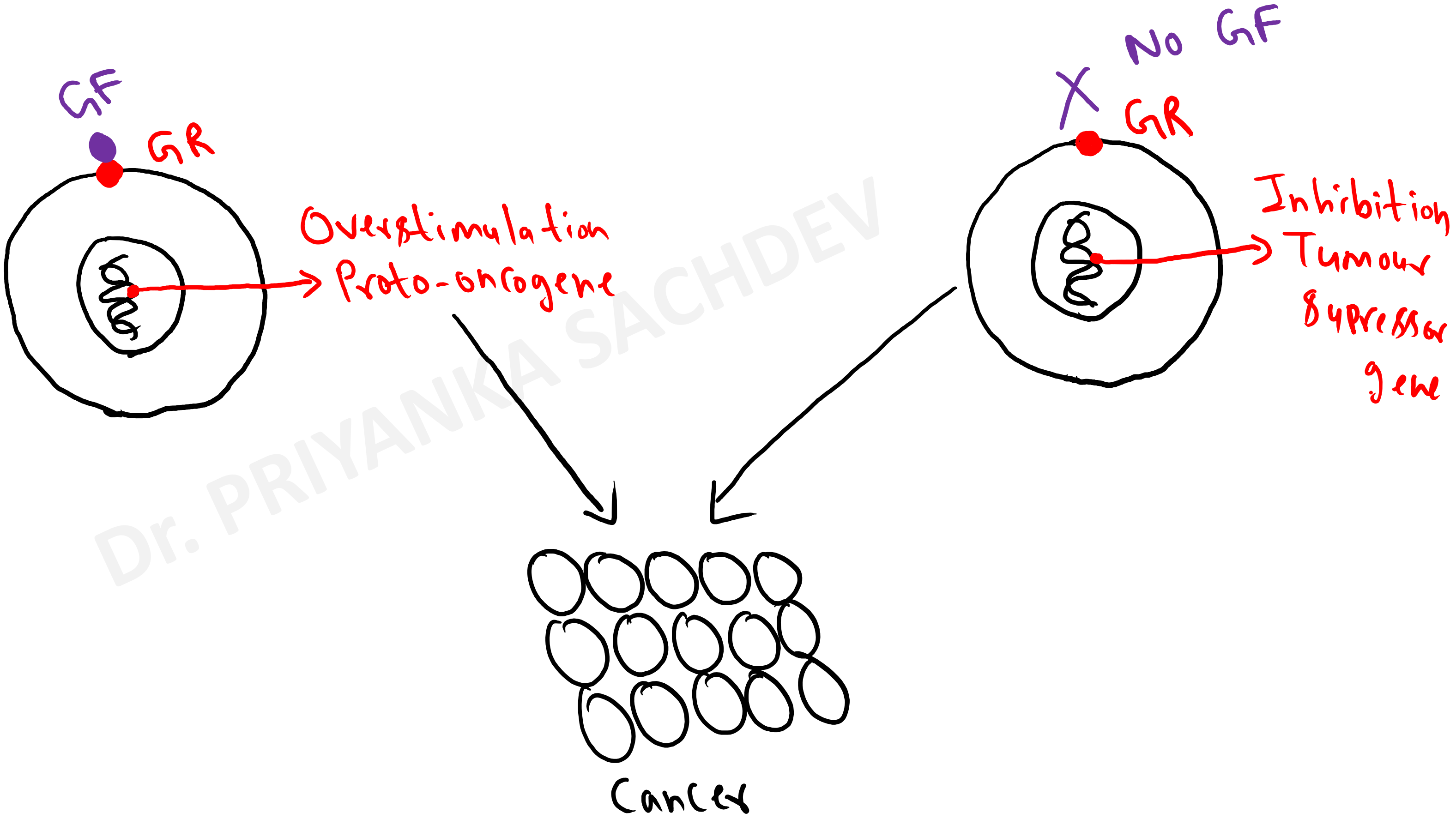
# 2. INACTIVATION OF Tumour sppressor genes

- Tumor suppressor genes are the genes whose products down regulate the cell cycle and **thus apply brakes to cellular proliferation**
- Normally tumour suppressor genes act by entering the cell into G0 (resting) phase
- So, **loss of function** of tumor suppressor genes results in uncontrolled cell proliferation and carcinogenesis.

# NORMAL CELL


GF
GR
Proto-oncogene
mitosis
No GF
GR
Tumour suppressor gene
No mitosis

# NORMAL CELL


GF
GR
Overstimulation
Proto-oncogene
No GF
GR
Inhibition
Tumour
Suppressor
gene
Cancer

The mechanisms of loss of tumour suppressor actions of genes are due to

1. **Chromosomal deletions**
2. **Point mutations**

# CLASSIFICATION

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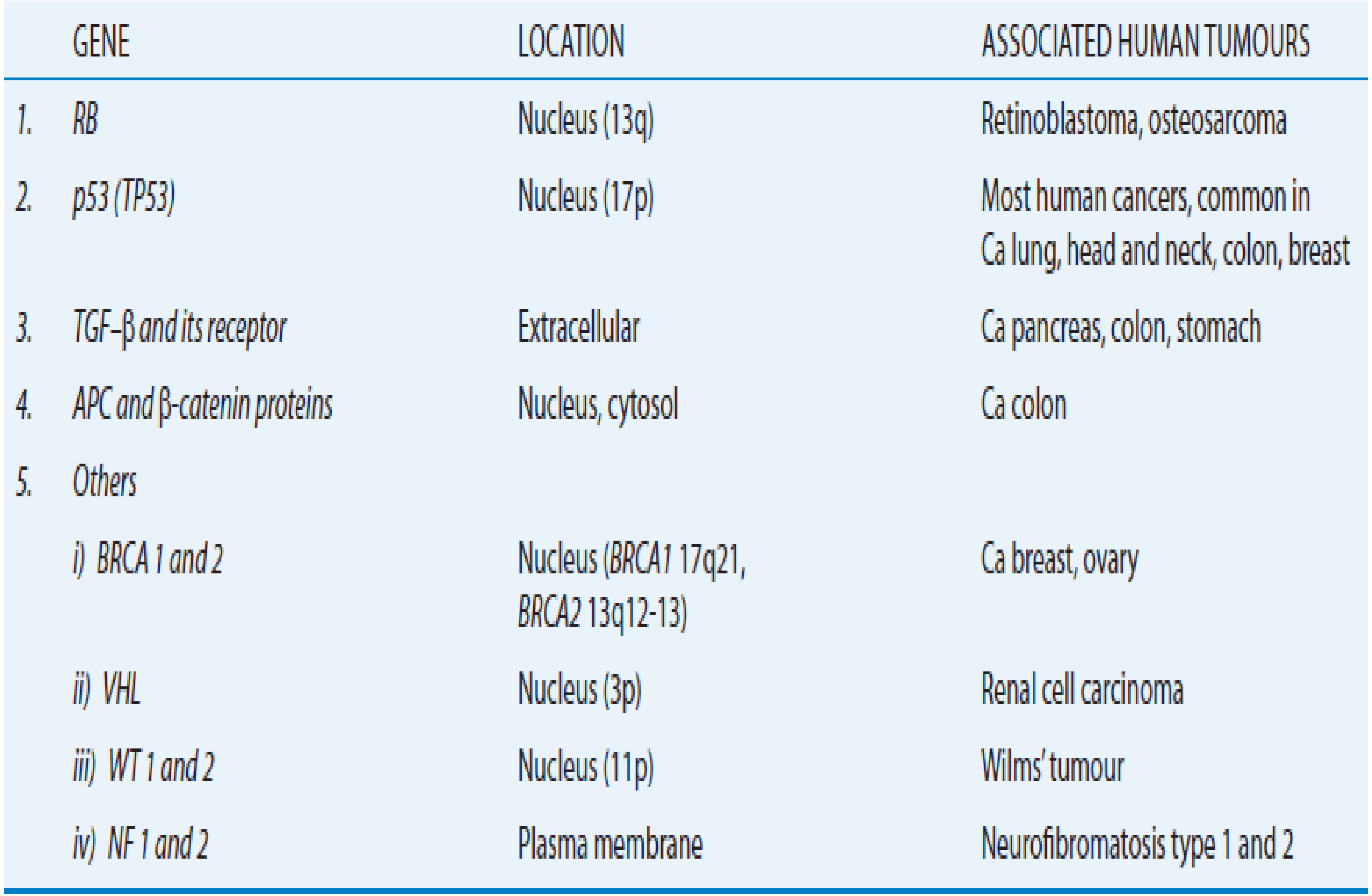


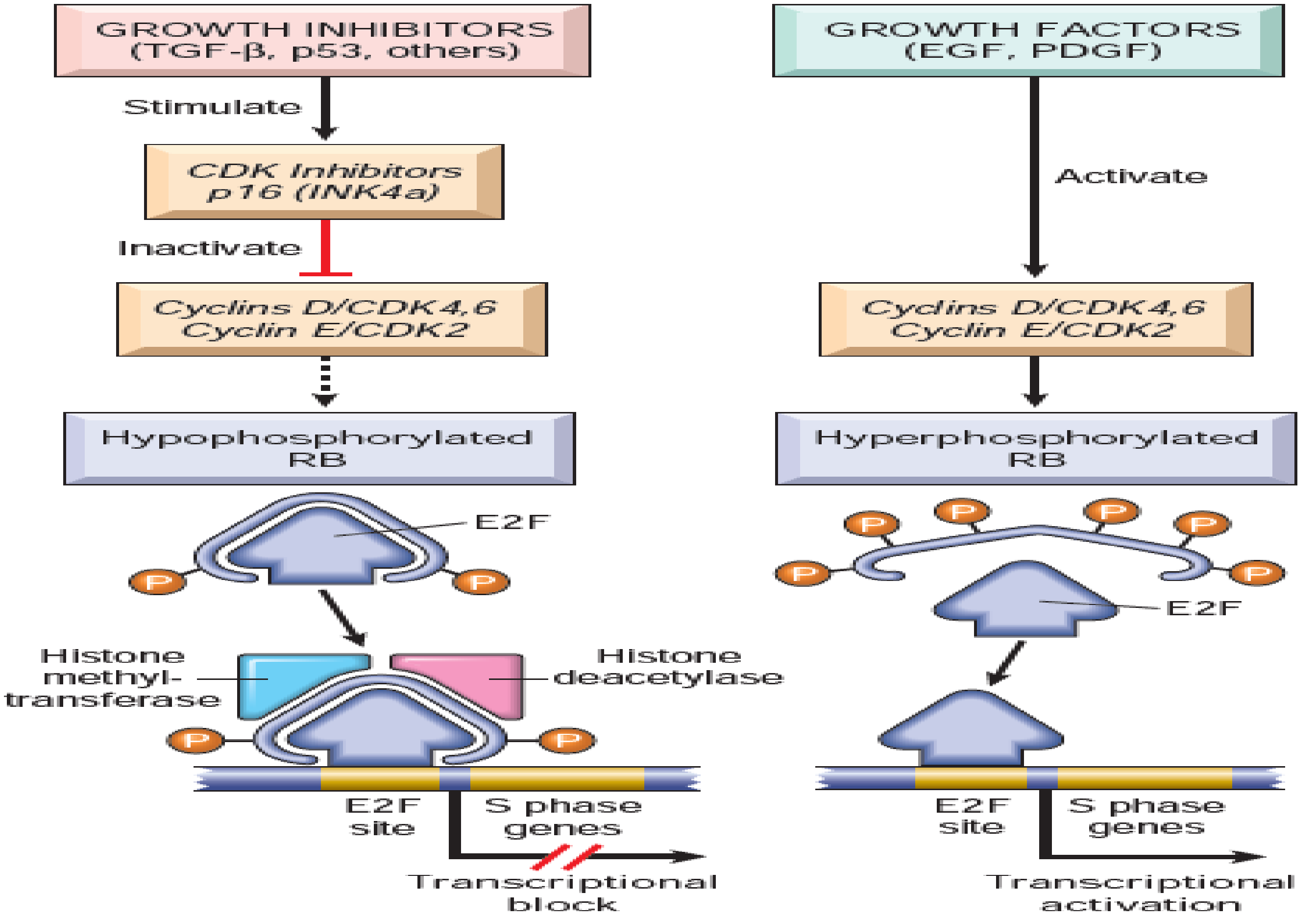
| | GENE | LOCATION | ASSOCIATED HUMAN TUMOURS |
|---|---|---|---|
| 1. | *RB* | Nucleus (13q) | Retinoblastoma, osteosarcoma |
| 2. | *p53 (TP53)* | Nucleus (17p) | Most human cancers, common in Ca lung, head and neck, colon, breast |
| 3. | *TGF–β and its receptor* | Extracellular | Ca pancreas, colon, stomach |
| 4. | *APC and β-catenin proteins* | Nucleus, cytosol | Ca colon |
| 5. | *Others* | | |
| | *i) BRCA 1 and 2* | Nucleus (*BRCA1* 17q21, *BRCA2* 13q12-13) | Ca breast, ovary |
| | *ii) VHL* | Nucleus (3p) | Renal cell carcinoma |
| | *iii) WT 1 and 2* | Nucleus (11p) | Wilms' tumour |
| | *iv) NF 1 and 2* | Plasma membrane | Neurofibromatosis type 1 and 2 |

# RB gene

- Located on long arm (q) of **chromosome 13 (chromosome 13q14)**

- RB gene was the **first tumor suppressor gene to be discovered**

# NORMALLY



GROWTH INHIBITORS
(TGF-β, p53, others)

Stimulate

*CDK Inhibitors*
*p16 (INK4a)*

Inactivate

*Cyclins D/CDK4,6*
*Cyclin E/CDK2*

Hypophosphorylated
RB

P

P

E2F

Histone
methyl-
transferase

Histone
deacetylase

P

P

E2F
site

S phase
genes

Transcriptional
block

GROWTH FACTORS
(EGF, PDGF)

Activate

*Cyclins D/CDK4,6*
*Cyclin E/CDK2*

Hyperphosphorylated
RB

P

P

P

P

P

P

E2F

E2F
site

S phase
genes

Transcriptional
activation

Growth inhibitors

↓

Activates CDK inhibitors and inactivates cyclins and CDKS

↓

Hypophosphorylation of RB

↓

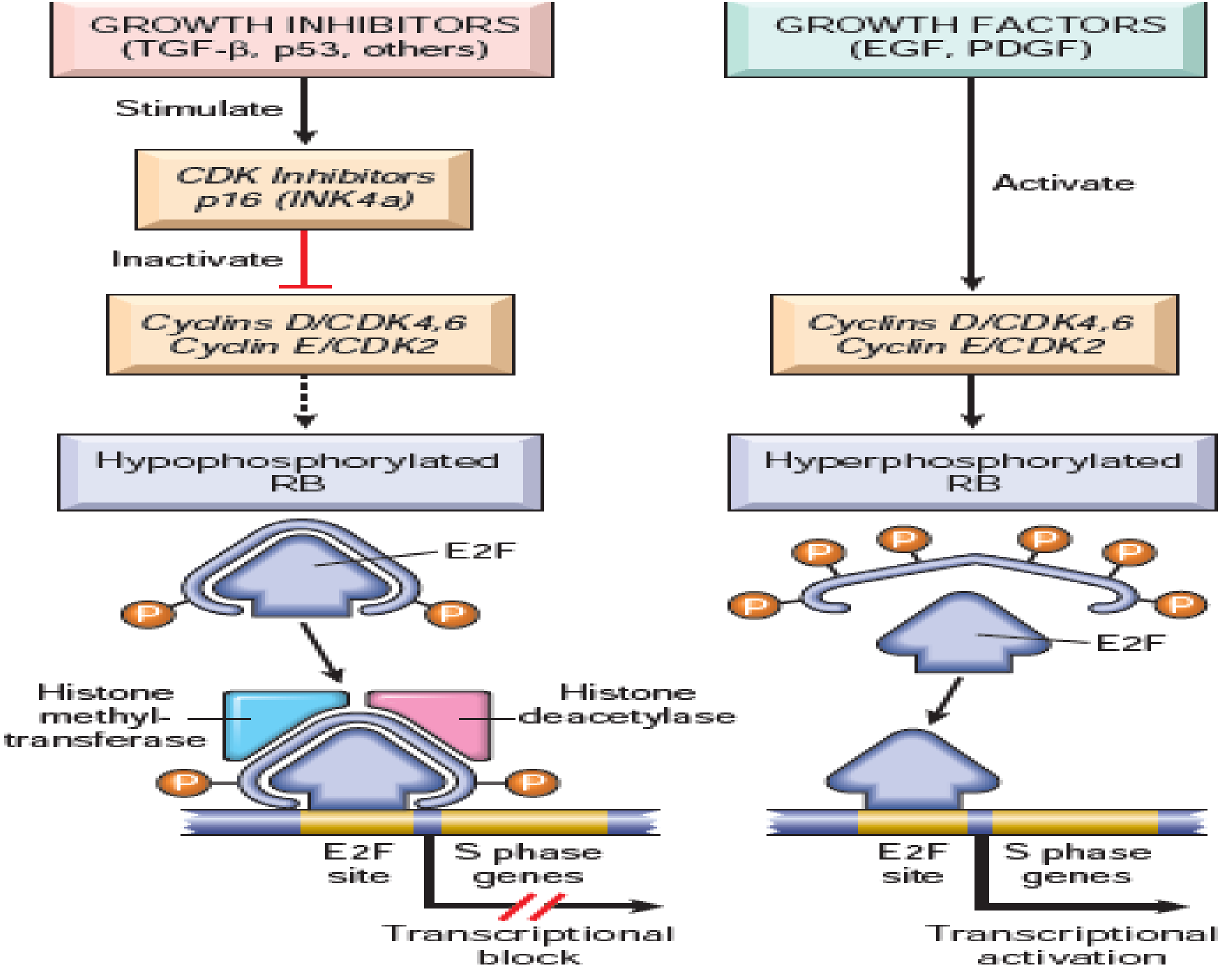
RB becomes active

↓

forming an inactive complex with transcription factor EF-2

↓

blocks cell division (no mitosis)


GROWTH INHIBITORS (TGF-β, p53, others)
Stimulate
CDK Inhibitors p16 (INK4a)
Inactivate
Cyclins D/CDK4,6 Cyclin E/CDK2
Hypophosphorylated RB
E2F
P
Histone methyl-transferase
Histone deacetylase
E2F site
S phase genes
Transcriptional block
GROWTH FACTORS (EGF, PDGF)
Activate
Cyclins D/CDK4,6 Cyclin E/CDK2
Hyperphosphorylated RB
P
E2F
E2F site
S phase genes
Transcriptional activation

Growth factors

↓

Activates cyclins and CDKS

↓

Hyperphosphorylation of RB

↓

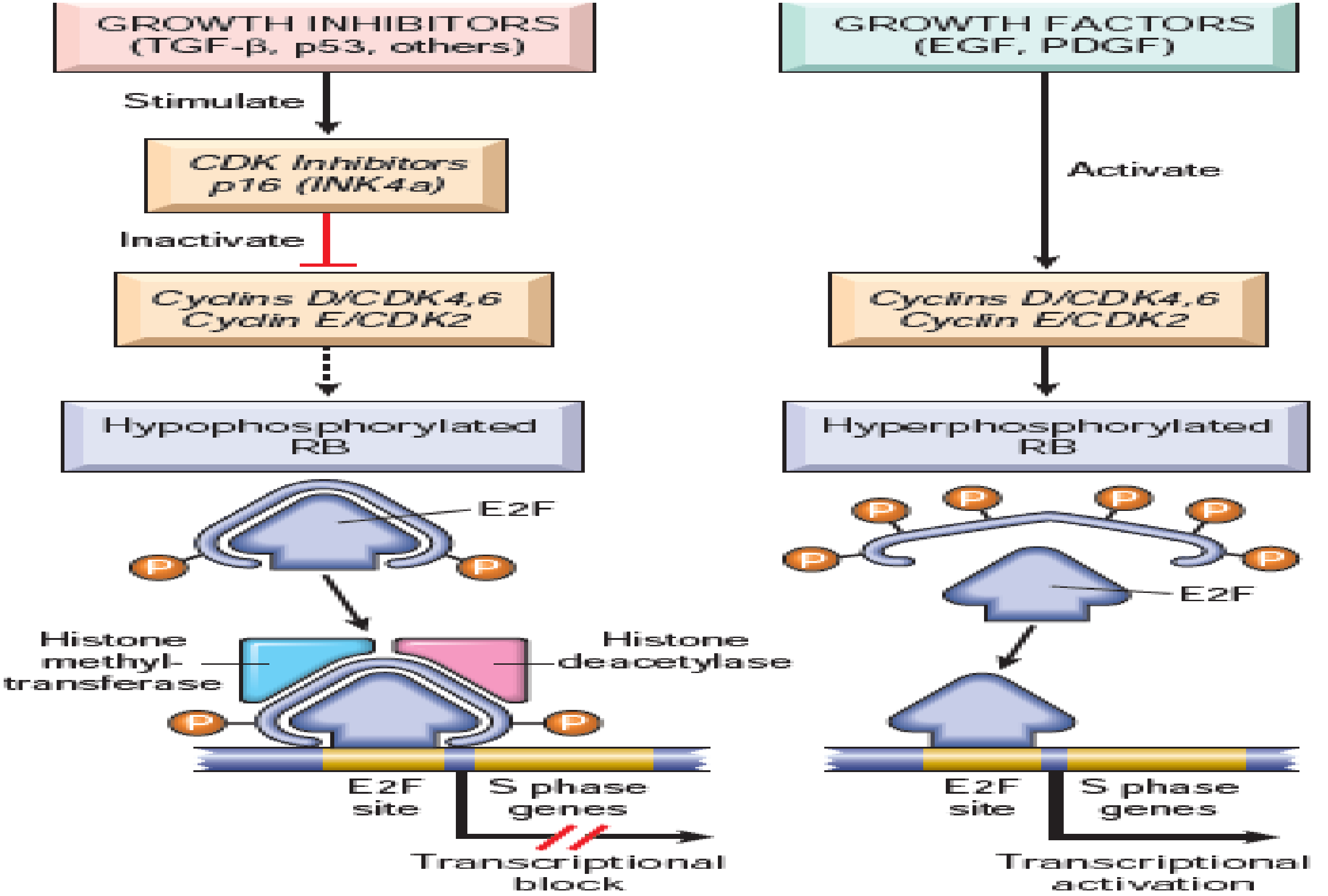
RB becomes inactive

↓

Dislocation of RB from transcription factor EF-2

↓

Cell division (mitosis)



GROWTH INHIBITORS
(TGF-β, p53, others)

Stimulate

*CDK Inhibitors*
*p16 (INK4a)*

Inactivate

*Cyclins D/CDK4,6*
*Cyclin E/CDK2*

Hypophosphorylated
RB

E2F
P
P
Histone methyl-transferase
Histone deacetylase
P
P
E2F site
S phase genes

Transcriptional
block

GROWTH FACTORS
(EGF, PDGF)

Activate

*Cyclins D/CDK4,6*
*Cyclin E/CDK2*

Hyperphosphorylated
RB

P
P
P
P
P
P
E2F
E2F site
S phase genes

Transcriptional
activation

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# Mutation in RB→

**Mutation in RB**

↓

**Permanent inactivation of RB**

↓

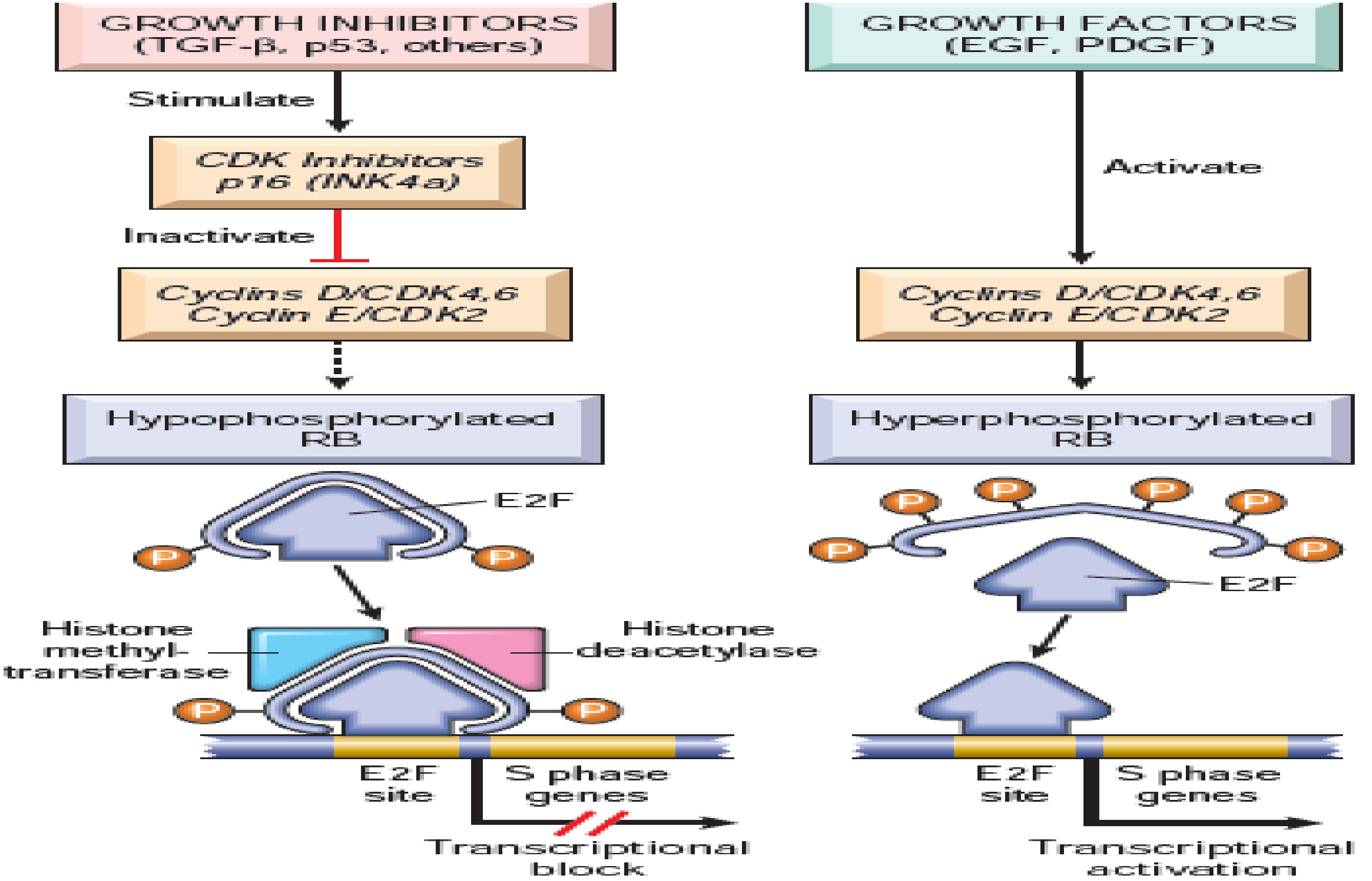
**Permanent Dislocation of RB from transcription factor EF-2**

↓

**Abnormal Cell division (mitosis)**

↓

**Cancer**



GROWTH INHIBITORS (TGF-β, p53, others)

Stimulate

*CDK Inhibitors p16 (INK4a)*

Inactivate

*Cyclins D/CDK4,6 Cyclin E/CDK2*

Hypophosphorylated RB

GROWTH FACTORS (EGF, PDGF)

Activate

*Cyclins D/CDK4,6 Cyclin E/CDK2*

Hyperphosphorylated RB

E2F
P
P
Histone methyl-transferase
Histone deacetylase
E2F site
S phase genes
Transcriptional block
P
E2F
E2F site
S phase genes
Transcriptional activation

**ACTIVE RB gene →**

- Active in hypophosphorylated state
- Prevents replication by forming an inactive complex with transcription factor EF-2
- blocks cell division
- Inhibiting the cell cycle at G1 → S phase

**INACTIVE RB gene→**

- Phosphorylation of RB gene causes inactivation of RB gene
- Dissociation of RB from EF-2
- Activation of EF-2
- Cell replication

**Mutation in RB→**

Permanent inactivation of RB

- Retinoblastoma is associated with concept of

1. **Loss of Heterozygosity**
2. **Knudson's Two Hit Hypothesis**

# Knudson's two hit hypothesis→

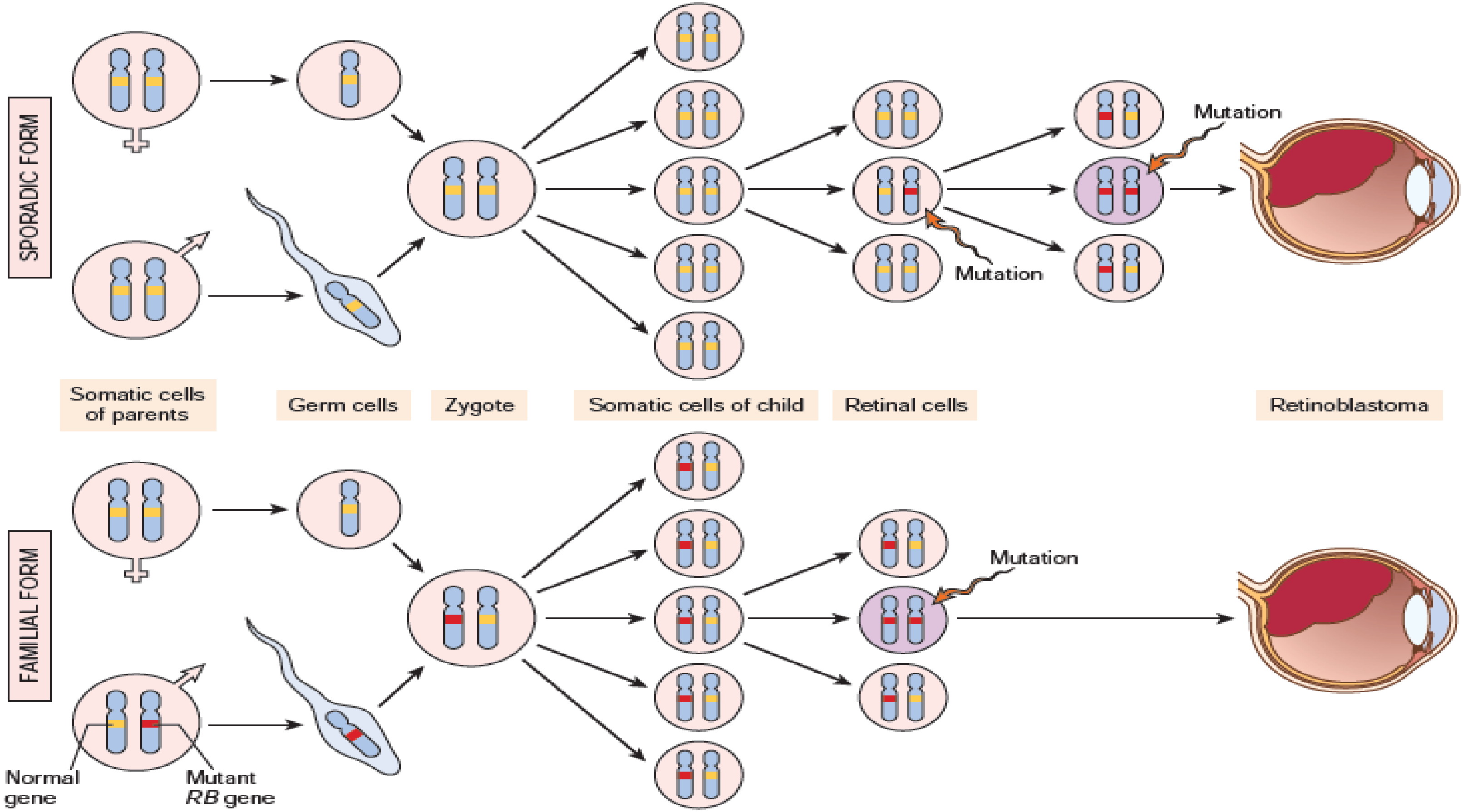
- Retinoblastoma develops when both the normal alleles of the RB genes are inactived

# Familial/Hereditary retinoblastoma

- First genetic change (first hit) in RB gene is inherited from an affected parent

- Second mutation (second hit) occurs in postnatal life and both alleles are lost.

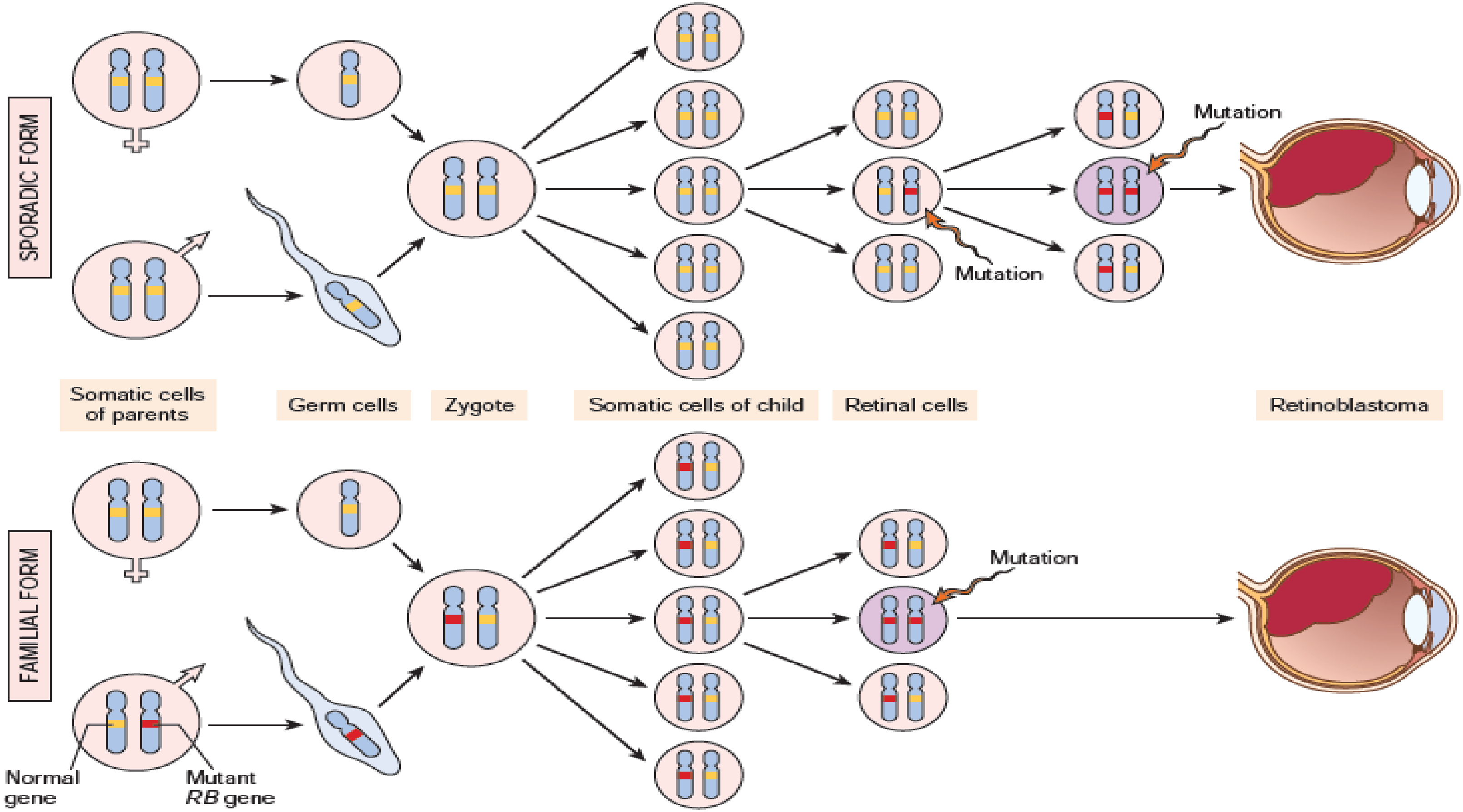
# PATHOGENESIS OF RETINOBLASTOMA


SPORADIC FORM
Mutation
Mutation
Somatic cells of parents
Germ cells
Zygote
Somatic cells of child
Retinal cells
Retinoblastoma
FAMILIAL FORM
Mutation
Normal gene
Mutant *RB* gene

- In hereditary retinoblastoma, children are born with one normal and one abnormal RB gene, i.e. **Heterozygous for RB gene.**

- Mutation in normal RB gene results in loss of heterozygosity (as both RB genes become abnormal) and development of retinoblastoma→ **Loss of Heterozygosity**

# PATHOGENESIS OF RETINOBLASTOMA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Retinoblastoma
FAMILIAL FORM
Mutation
Normal gene
Mutant *RB* gene

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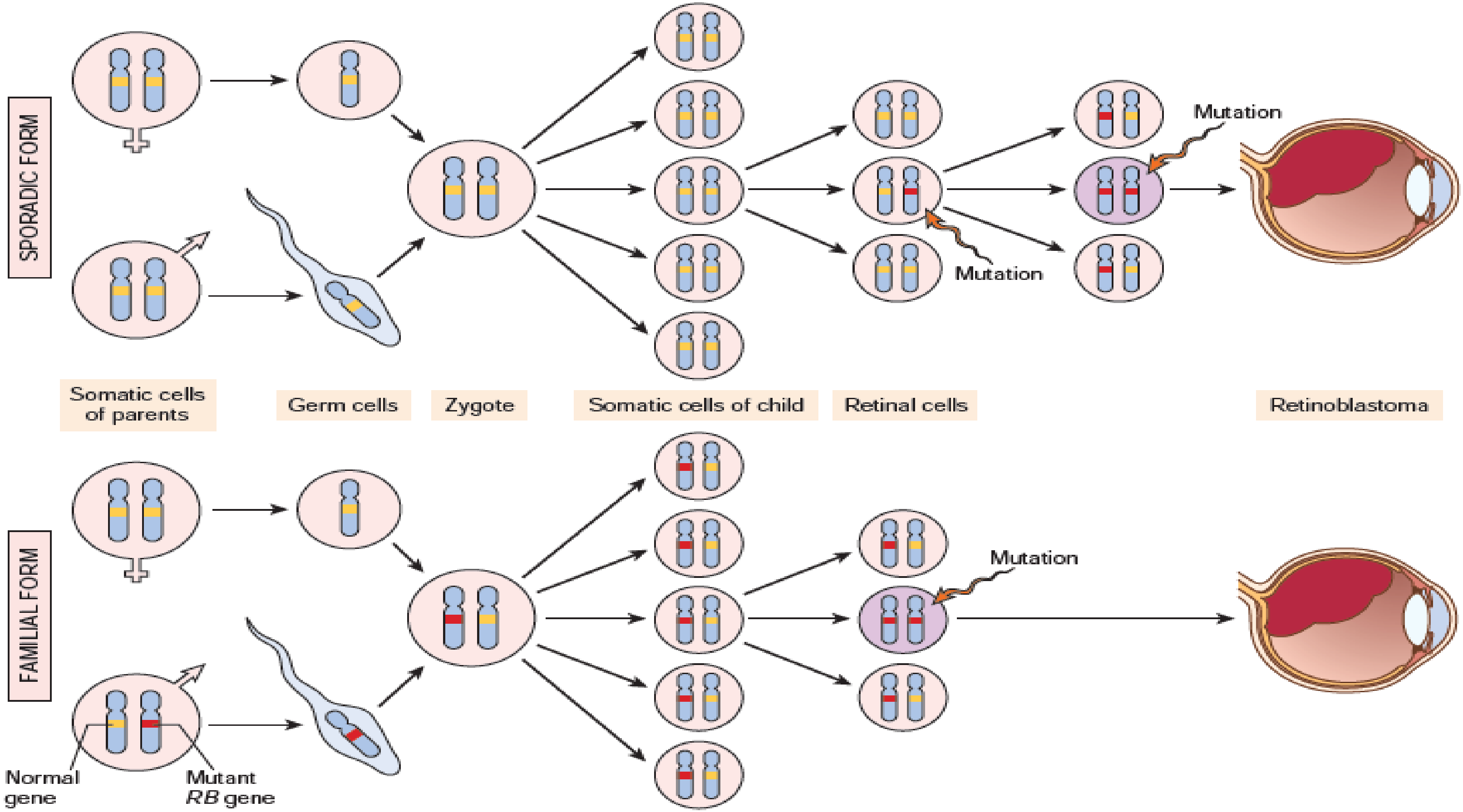
# Sporadic/non- hereditary retinoblastoma

- Both mutations (first and second hits) occur postnataly

# PATHOGENESIS OF RETINOBLASTOMA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Mutation
Mutation
Somatic cells of parents
Germ cells
Zygote
Somatic cells of child
Retinal cells
Retinoblastoma
FAMILIAL FORM
Mutation
Normal gene
Mutant *RB* gene

## Familial retinoblastoma

- comprises 40% of cases
- bilateral.
- **somatic cells inherit one mutant RB gene from a carrier parent (i.e. germline mutation). The other mutation occurs after birth.**
- Besides retinoblastoma, children inheriting mutant RB gene have **200 times greater risk of development of other cancers eg osteosarcoma, breast, colon and lungs.**

## Sporadic retinoblastoma

- constitutes 60% of cases
- unilateral.
- **acquired both the somatic mutations in the two alleles after birth.**

- Familial Retinoblastoma is also associated with increased risk of osteosarcomas.

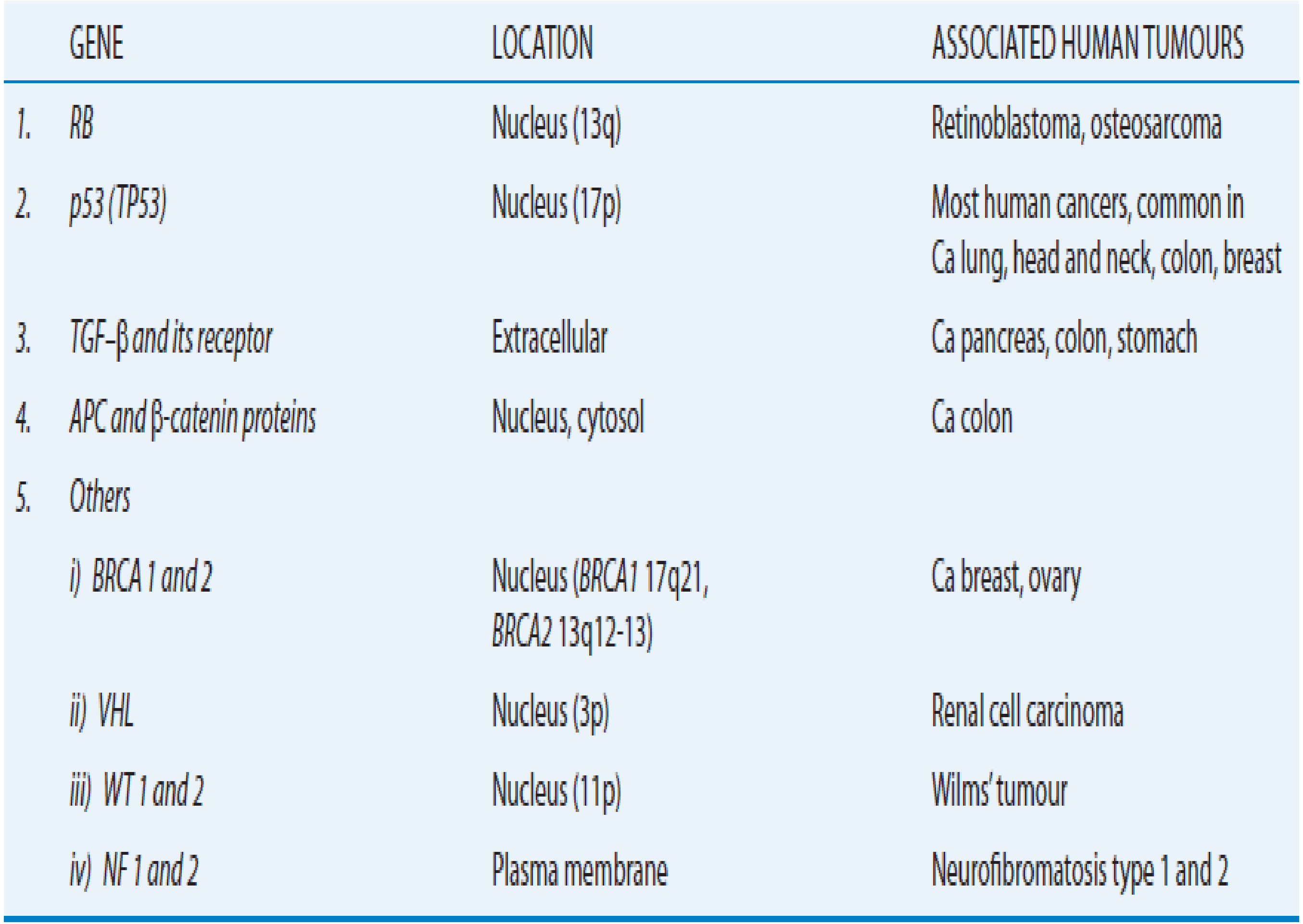
# REMEMBER

- Retinoblastoma is associated with Concept of Loss of Heterozygosity as well as Knudson’s Two Hit Hypothesis

- **Retinoblastoma is the most common primary intraocular malignancy of children.**

- In the sporadic cases, both RB allelesare lost by somatic mutations.

- Retinoblastomas arising in the context of germline mutations are often bilateral.
- In addition, they may be associated with pinealoblastoma **("trilateral" retinoblastoma**).



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| | *iv) NF 1 and 2* | Plasma membrane | Neurofibromatosis type 1 and 2 |

# P53 gene

- p53 is a **tumor suppressor gene.**
- p53 gene is located on **chromosome 17**
- **Guardian of genome**
- **Molecular policeman**

- P53 is a tumour suppressor gene as well as DNA repair gene

# In cancer

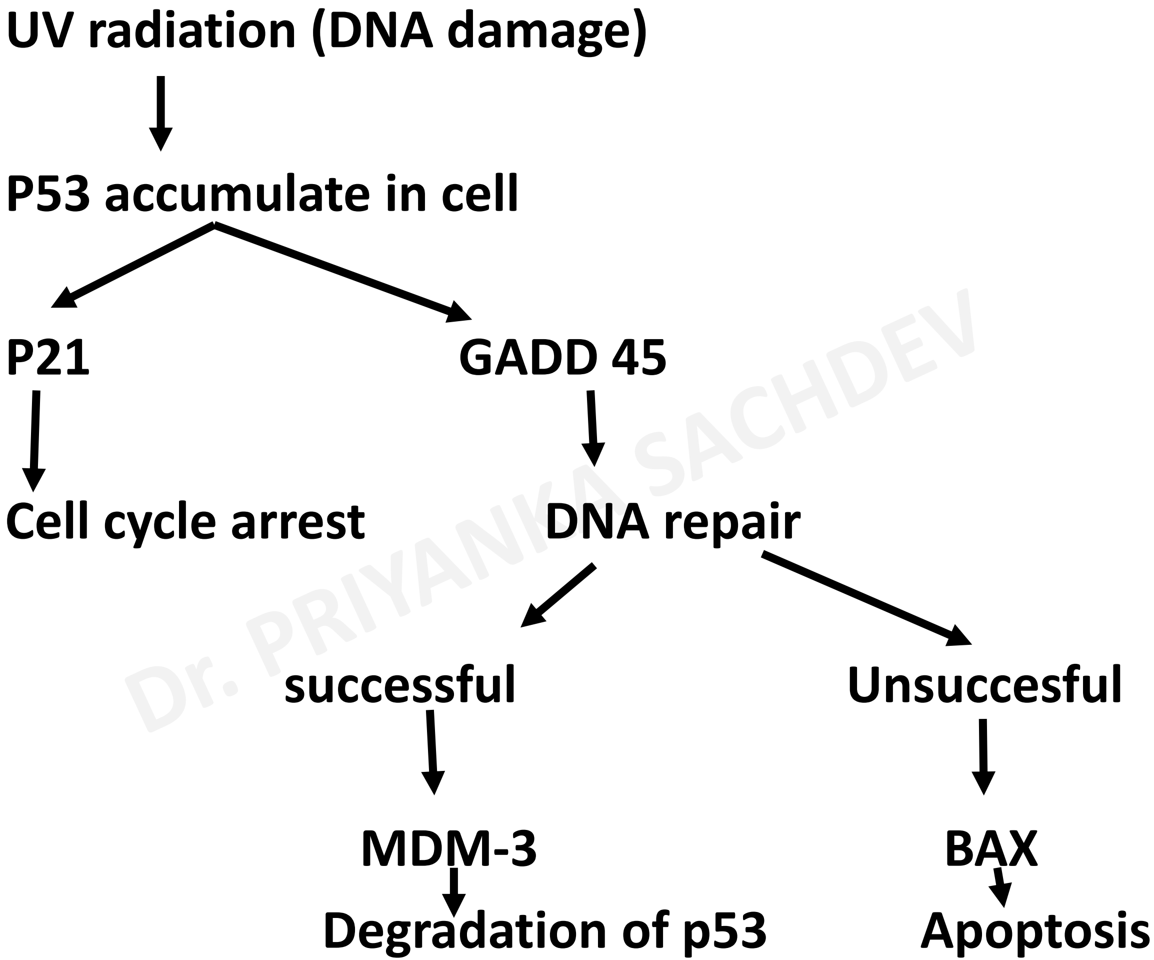
i) Activation of proto-oncogenes

ii) Inactivation of tumour-suppressor genes

iii) Abnormal apoptosis regulatory genes

iv) Inactivation of DNA repair genes

# NORMALLY



UV radiation (DNA damage)

P53 accumulate in cell

P21

Cell cycle arrest

GADD 45

DNA repair

successful

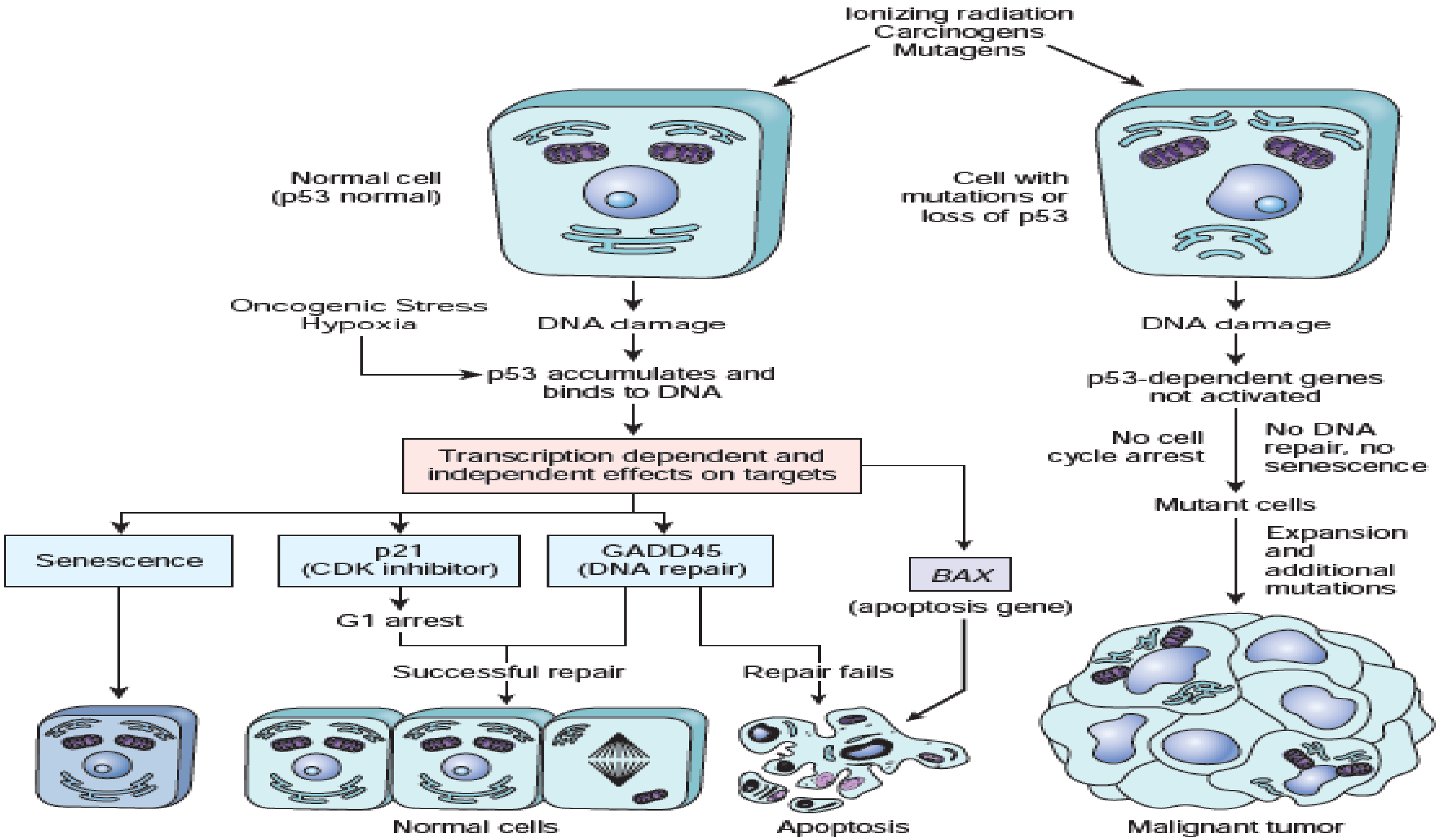
MDM-3

Degradation of p53

Unsuccesful

BAX

Apoptosis



Ionizing radiation
Carcinogens
Mutagens

Normal cell
(p53 normal)

Cell with
mutations or
loss of p53

Oncogenic Stress
Hypoxia

DNA damage

p53 accumulates and
binds to DNA

Transcription dependent and
independent effects on targets

Senescence

p21
(CDK inhibitor)

G1 arrest

GADD45
(DNA repair)

*BAX*
(apoptosis gene)

Successful repair

Repair fails

Normal cells

Apoptosis

DNA damage

p53-dependent genes
not activated

No cell
cycle arrest

No DNA
repair, no
senescence

Mutant cells

Expansion
and
additional
mutations

Malignant tumor

- **p53 acts through: CDK inhibitor p21**
- p53 itself is not a CDK inhbitor

# Mutation in p53

**Cells with mutation or loss of p53**

↓

**DNA damage**

↓

**p53 dependent genes not activated**

↓

**No cell cycle arrest**

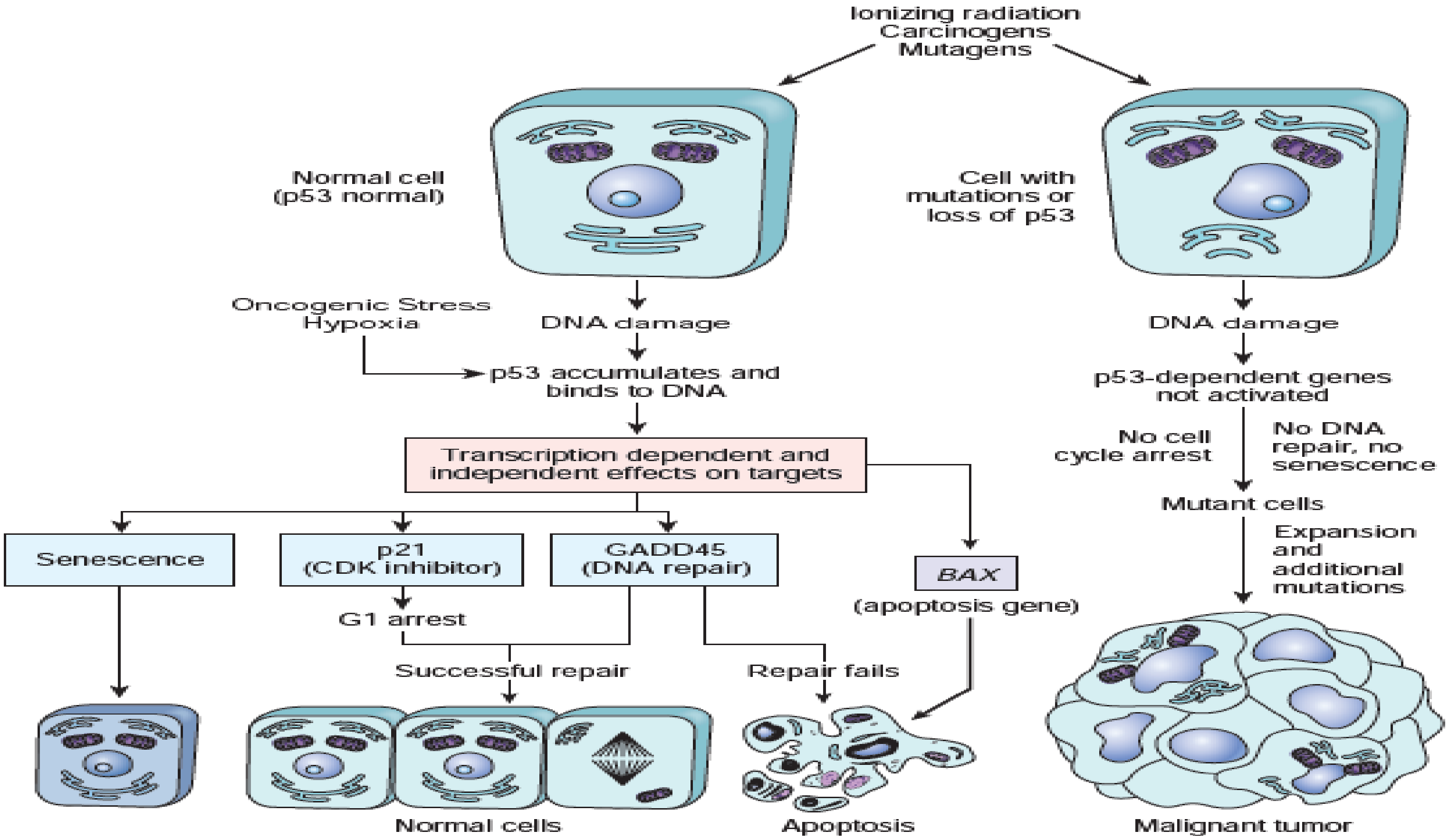
**No DNA repair**

↓

**Mutant cells→Expansion and additional mutations**

↓

**Cancer**



Ionizing radiation
Carcinogens
Mutagens

Normal cell
(p53 normal)

Cell with
mutations or
loss of p53

Oncogenic Stress
Hypoxia

DNA damage

p53 accumulates and
binds to DNA

Transcription dependent and
independent effects on targets

Senescence

p21
(CDK inhibitor)

G1 arrest

GADD45
(DNA repair)

Successful repair

Repair fails

*BAX*
(apoptosis gene)

Normal cells

Apoptosis

DNA damage

p53-dependent genes
not activated

No cell
cycle arrest

No DNA
repair, no
senescence

Mutant cells

Expansion
and
additional
mutations

Malignant tumor

- When there is DNA damage due to irradiation, UV light or mutagenic chemicals, there is rapid increase in p53 levels.
- p53 causes→

## i) Cell cycle arrest:

- p-53 induces transcription of p21, a CDK inhibitor.
- p21 inhibit cyclin D-CDK-4 complex
- arrest of cell cycle in G1 phase.
- This allow time for DNA repair.

## ii) DNA repair:

- inducing transcription of GADD 45 (growth arrest and DNA damage).
- GADD 45 encodes a protein that is involved in DNA repair.

**If DNA damage is repaired successfully,**

- p53 activate MDM-3
- MDM-3 induce degradation of p-53→ Relieve in cell cycle block

**If DNA damage cannot be successfully repaired,**

- p53 induces apoptosis by inducing the activation of apoptosis inducing gene BAX
- **So p-53 prevents replication of cell with defective DNA**

# REMEMBER

- **Non-mutated (wild type)** p53 reduces the chances of cancer.

- **Mutated form** is associated with cancer

- Sometimes individual may inherit one mutant p53 allele and the second acquired 'hit' may inactivate the normal p53 allele.
- This later condition is called **Li-Fraumeni syndrome**
- Associated with development of **sarcoma, breast cancer, leukemia and brain tumors.**

- **Human papilloma virus (HPV)** causes inactivation of p53 through its **E6 protein**

- so,it is responsible for development of cancer of anal and genital region.

- p73 (big brother of p53) and p63 are other members of the family of p53 gene.
- **p63** is esential for the **differentiation of stratified squamous epithelia.**
- **p73** has **pro-apoptotic effects after DNA damage induced by the chemotherapeutic agents**

# REMEMBER

- **Overall** → **p-53**
- Amongst **Tumour suppressor genes**→ **p-53** is involved most commonly
- Amongst **Proto-oncogene** → **RAS** is involved most commonly

# POLLS 2

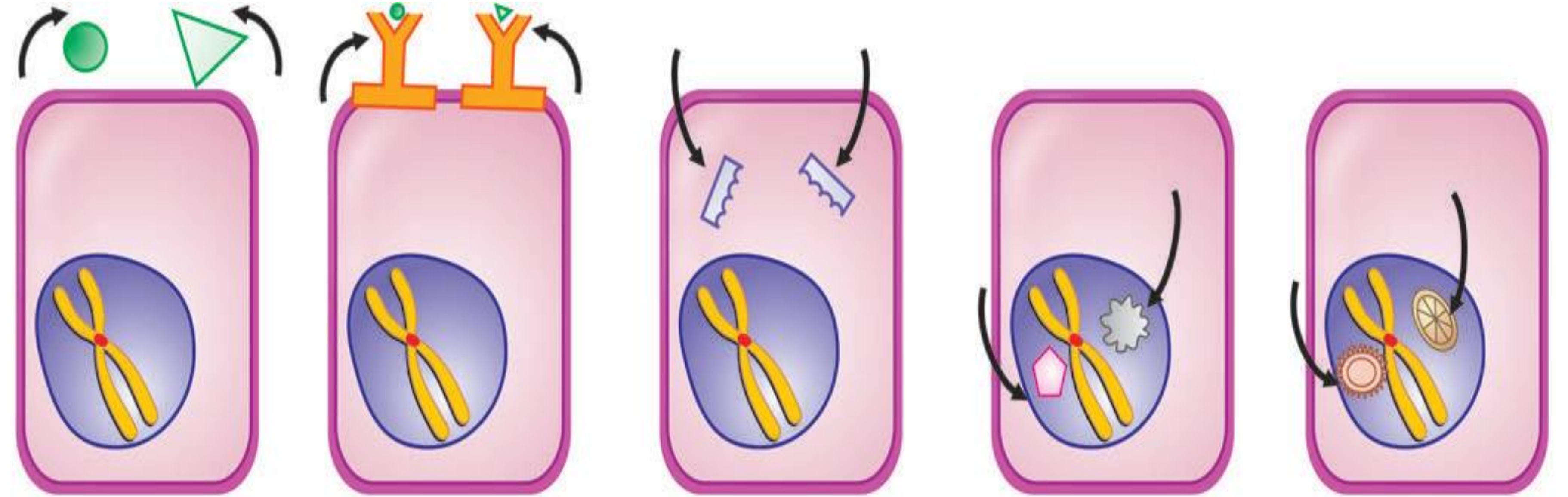
Scan or Click to watch
Neoplasia E01

Scan or Click to watch
Neoplasia E02

# An example of a tumour suppressor gene is -

- a) myc
- b) EGFR
- c) ras
- d) Rb

# D



| GROWTH FACTORS | RECEPTORS FOR GFs | CYTOPLASMIC SIGNAL TRANSDUCTION PROTEINS | NUCLEAR TRANSCRIPTION FACTORS | CELL CYCLE REGULATORY PROTEINS |
|---|---|---|---|---|
| i) PDGF-β<br>ii) TGF-α<br>iii) FGF<br>iv) c-MET | i) EGF-R<br>ii) c-KIT -R<br>iii) RET-R<br>iv) FMS-like | I) Mutated RAS<br>ii) ABL-BCR | i) C-MYC<br>ii) N-MYC<br>iii) L-MYC | i) Cyclin D<br>ii) Cyclin E<br>iii) CDK4 |

**Dr. PRIYANKA SACHDEV**

**Carcinoma due to inherited mutation of p53 protooncogene -**

a) Li fraumeni syndrome
b) Familial adenomatous polyposis
c) Retinoblastoma
d) Osteosarcoma

# A

**Hereditary retinoblastomas develop the following chromosomal deletion [Rb Gene location]-**

a) 13q14
b) 13p14
c) 14p13
d) 14p13

Dr.

# A

**A child is born with a single functional copy of a tumor suppressor gene. At the age of 5 years, the remaining normal allele is lost through mutation. As a result, the ability to control the transition from G1 to the S phase of the cell cycle is lost. Which of the following neoplasms is most likely to arise by means of this mechanism -**

a) Retinoblastoma
b) Breast carcinoma
c) Adenocarcinoma of colon
d) Cerebral astrocytoma

**Dr. PRIYANKA SACHDEV**

# A

**Loss of hetrozygosity associated with -**

a) Acute myeloid leukemia
b) ALL
c) Retinoblastoma
d) Promyelocitic leukemia

Dr.

# c

**The most common secondary malignancy in a patient having retinoblastoma is:**

(a) Osteosarcoma
(b) Renal cell carcinoma
(c) Pineoblastoma
(d) Osteoblastoma

Dr. PRI...

# A

## Which is not a tumor suppressor gene?

(a) WT-1

(b) Rb

(c) p53

(d) ras

Dr. PRI

# D

The inheritance pattern of familial Retinoblastoma is:

(a) Autosomal recessive
(b) Autosomal dominant
(c) X-linked dominant
(d) X-linked recessive

Dr. PRI

# B

Retinoblastoma is a prime example of a tumor which is associated with loss of heterozygosity.

- Rb gene is a tumor suppressor gene located on chromosome **13 q14Q.**
- Retinoblastoma develops when both the normal alleles of the Rb gene are inactivated or altered.
- Familial retinoblastoma is associated with **autosomal dominant inheritance** whereas the Rb gene is having **autosomal recessive inheritance.**

**Which of the following is known as the "guardian of the genome"?**

(a) p53
(b) Mdm2
(c) p14
(d) ATM

Dr. PRIYAN

# A

**The following statements are true about Tumor Suppressor Gene p53, except:**

(a) It regulates certain genes involved in cell cycle regulation

(b) Its increased levels can induce apoptosis

(c) Its activity in the cells decreases following UV irradiation and stimulates cell cycle

(d) Mutations of the p53 gene are most common genetic alteration seen in human cancer

# c

**Tumor suppressor genes are all, except**

(a) APC
(b) p53
(c) Rb
(d) C-myc

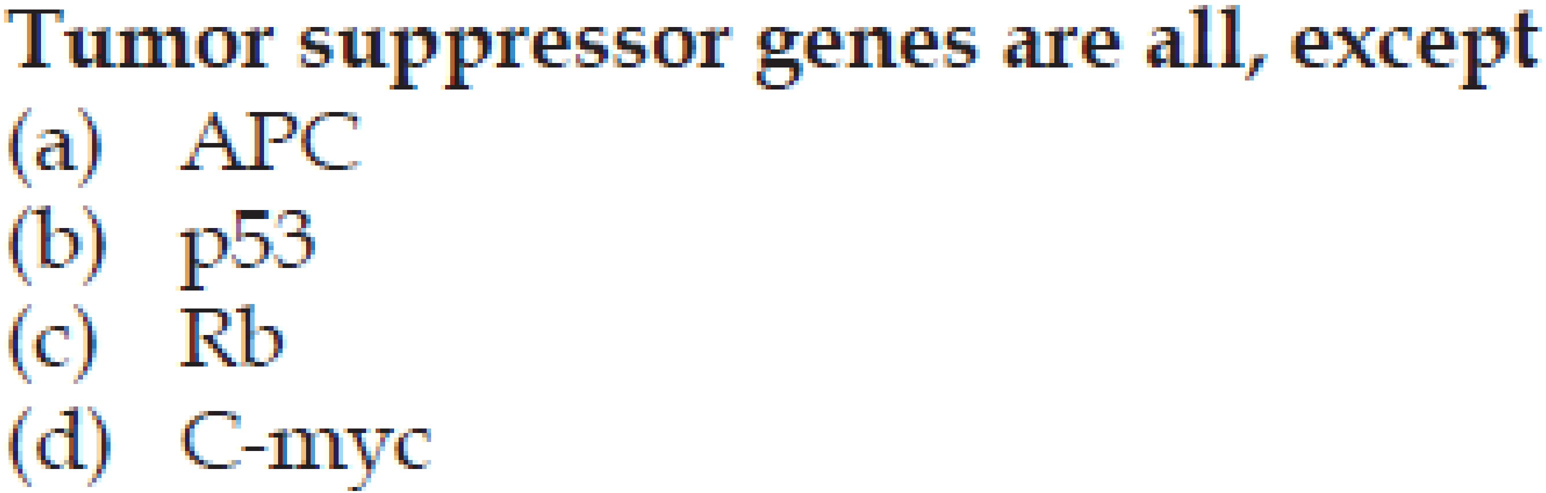
Dr. PRIY

# D

# Knudson two hit hypothesis is seen with

- (a) Melanoma
- (b) Retinoblastoma
- (c) Ulcerative colitis
- (d) Crohn disease

# B



**Tumor suppressor genes are all, except**

(a) APC

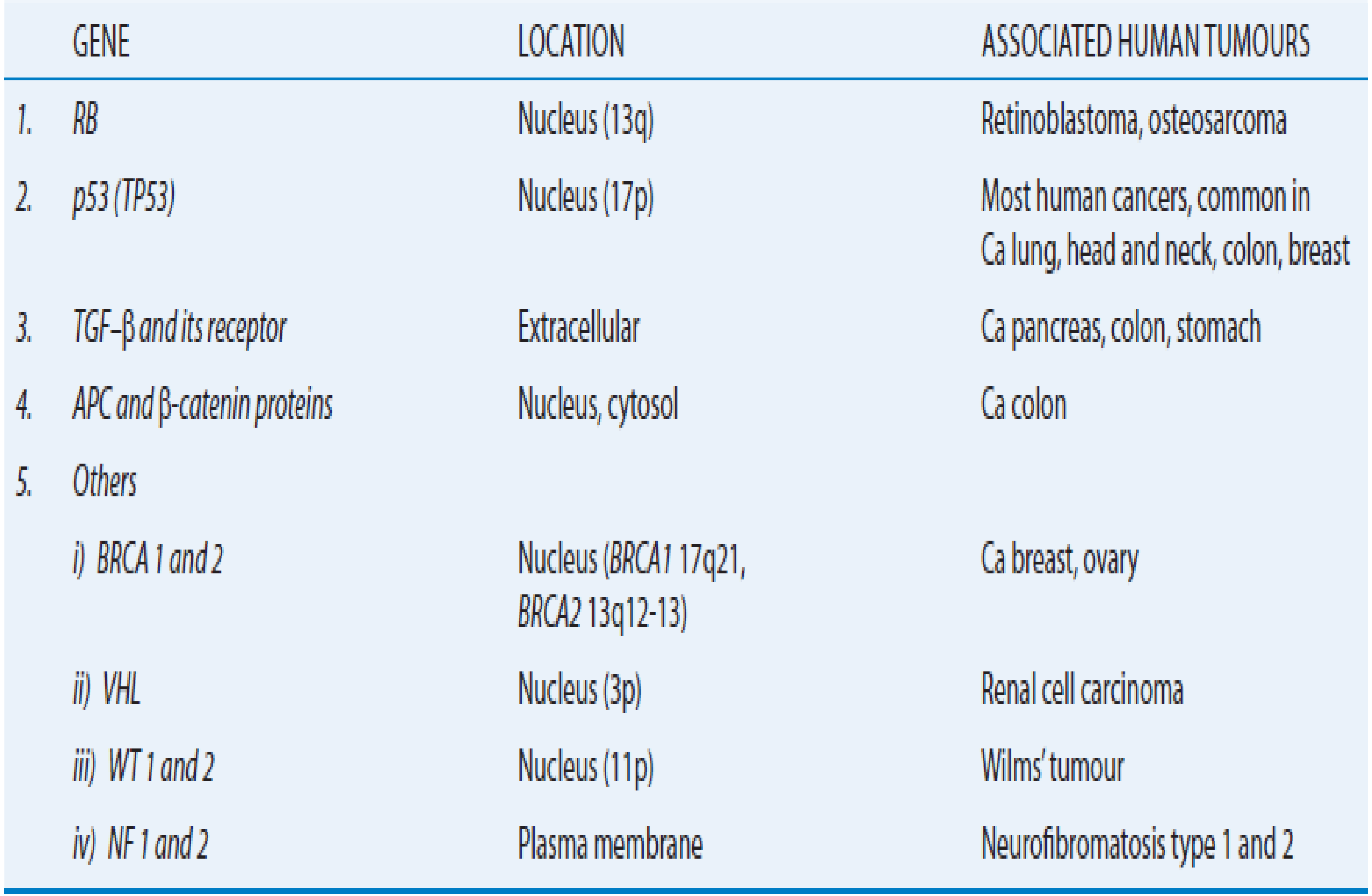
(b) p53

(c) Rb

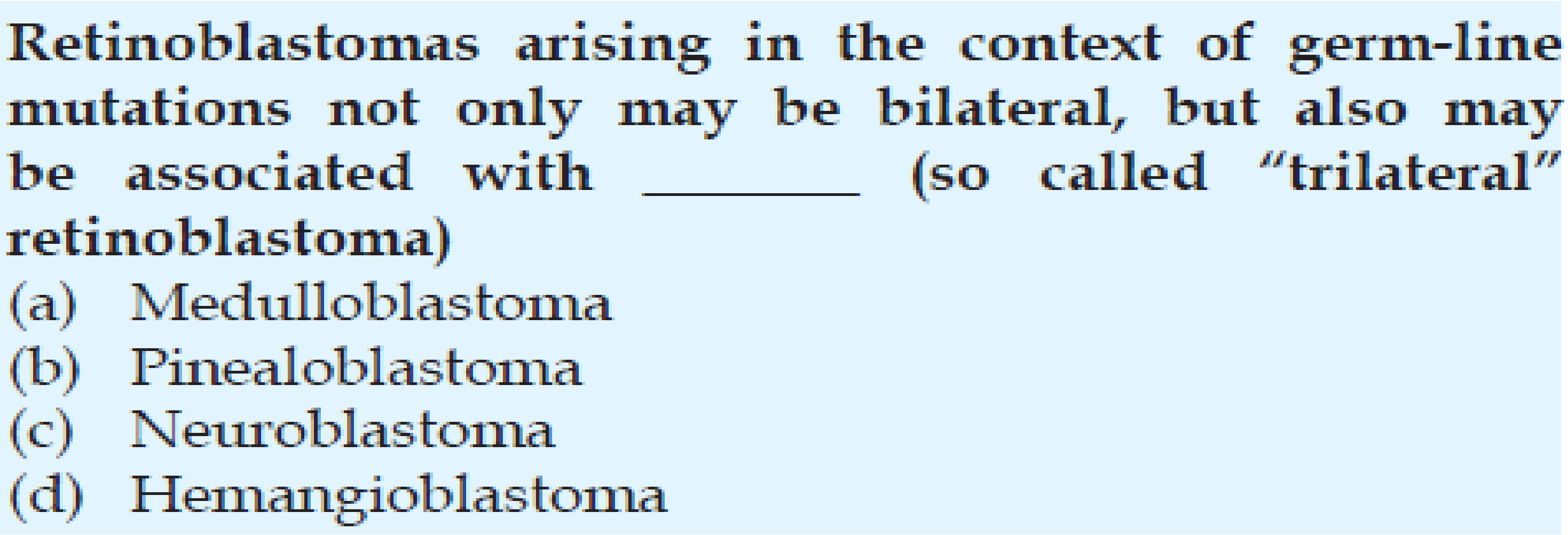
(d) C-myc

Dr. PRI

# D



| | GENE | LOCATION | ASSOCIATED HUMAN TUMOURS |
|---|---|---|---|
| 1. | *RB* | Nucleus (13q) | Retinoblastoma, osteosarcoma |
| 2. | *p53 (TP53)* | Nucleus (17p) | Most human cancers, common in Ca lung, head and neck, colon, breast |
| 3. | *TGF–β and its receptor* | Extracellular | Ca pancreas, colon, stomach |
| 4. | *APC and β-catenin proteins* | Nucleus, cytosol | Ca colon |
| 5. | *Others* | | |
| | *i) BRCA 1 and 2* | Nucleus (*BRCA1* 17q21,<br>*BRCA2* 13q12-13) | Ca breast, ovary |
| | *ii) VHL* | Nucleus (3p) | Renal cell carcinoma |
| | *iii) WT 1 and 2* | Nucleus (11p) | Wilms' tumour |
| | *iv) NF 1 and 2* | Plasma membrane | Neurofibromatosis type 1 and 2 |



**Retinoblastomas arising in the context of germ-line mutations not only may be bilateral, but also may be associated with ________ (so called "trilateral" retinoblastoma)**

(a) Medulloblastoma

(b) Pinealoblastoma

(c) Neuroblastoma

(d) Hemangioblastoma

Dr. PRI

# B

# REVISION

# In cancer

i) Activation of proto-oncogenes

ii) Inactivation of tumour-suppressor genes

iii) Abnormal apoptosis regulatory genes

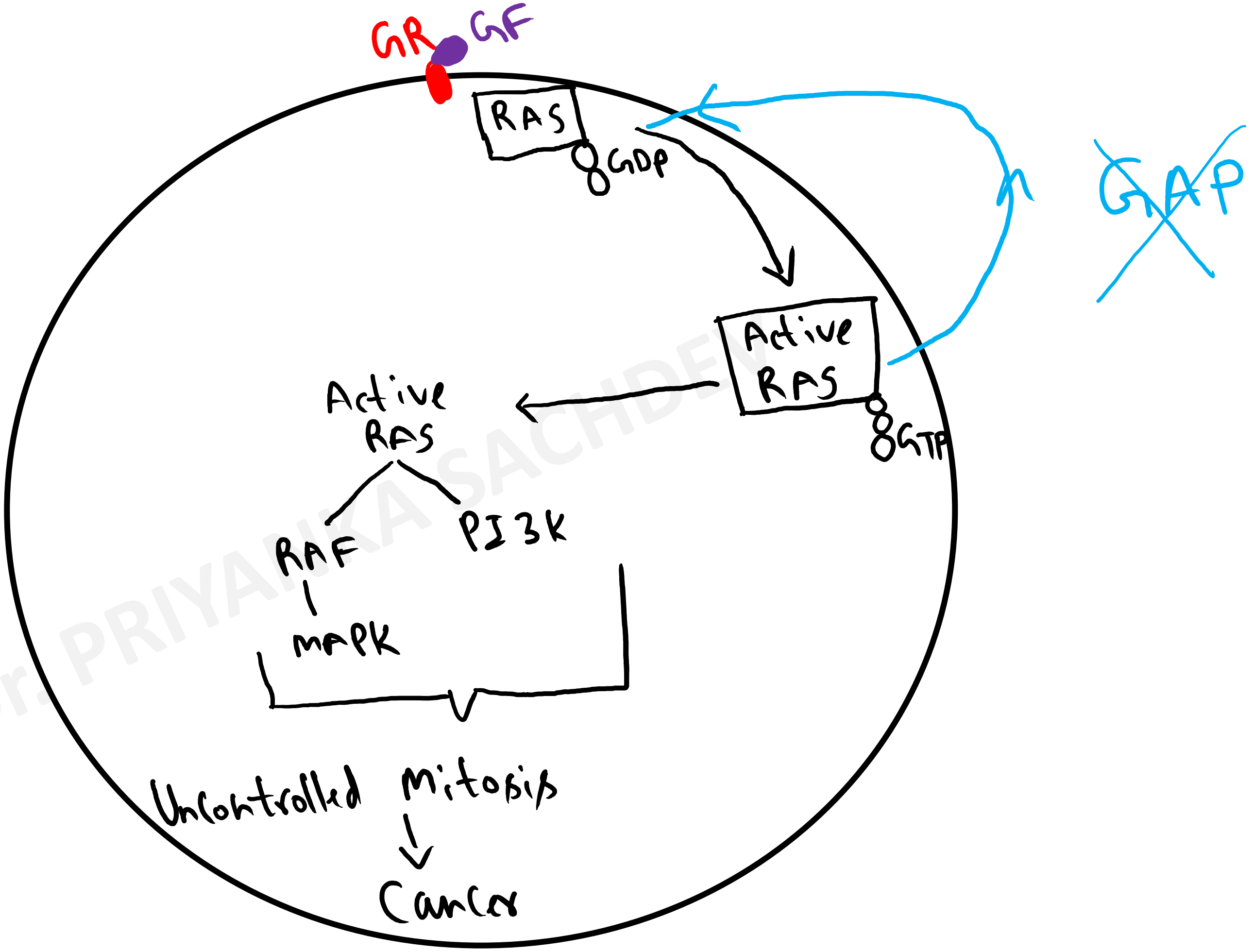
iv) Inactivation of DNA repair genes

# Activation of Proto-Oncogenes

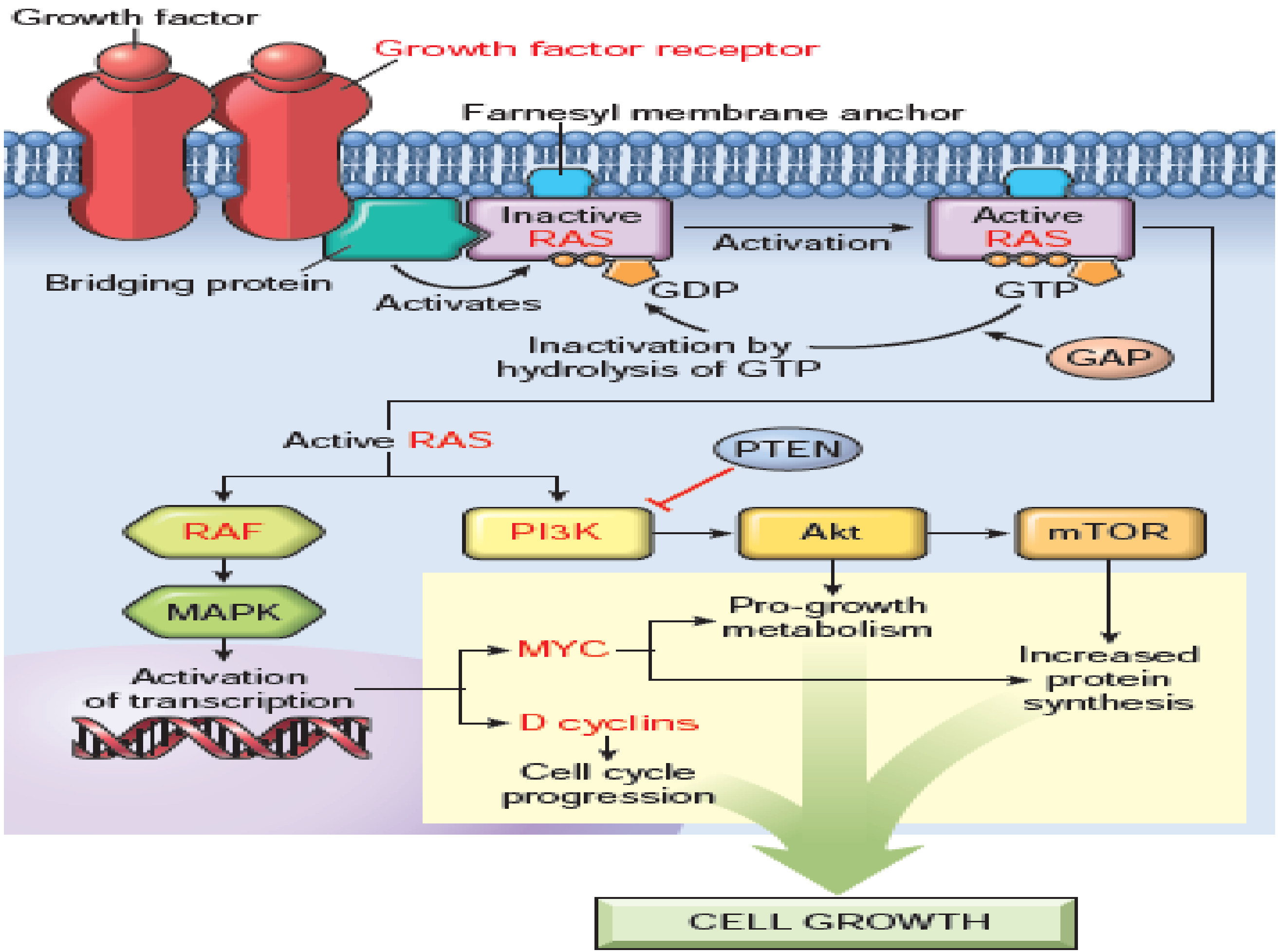
# RAS gene

- RAS protein is **signal transducing protein**

- Point mutation of RAS family genes is the single **most common abnormality of Proto-oncogenes** in human tumor.


GR
GF
RAS
GDP
Active RAS
GTP
~~GAP~~
Active RAS
RAF
PI3K
MAPK
Uncontrolled Mitosis
Cancer

Dr. PRIYANKA SACHDEV

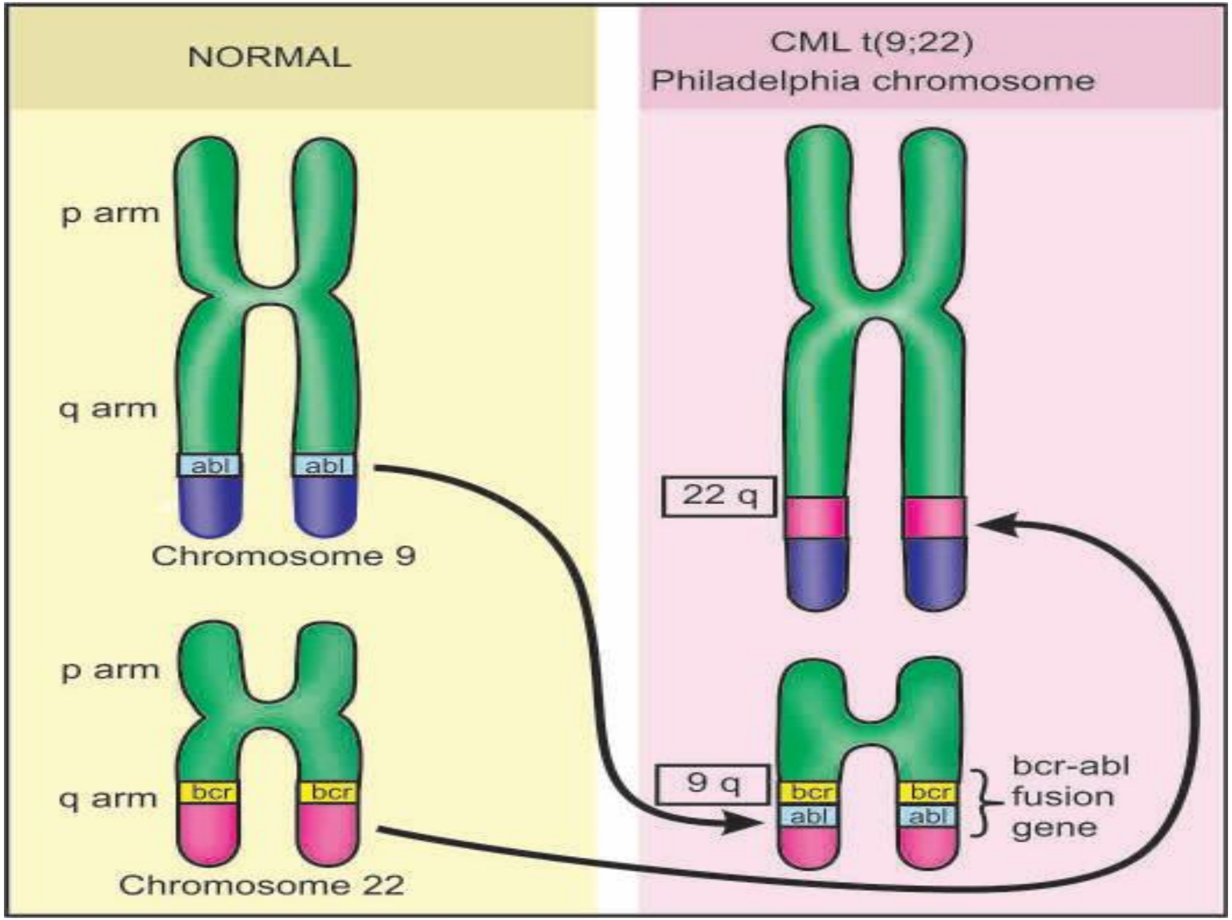

Growth factor
Growth factor receptor
Farnesyl membrane anchor
Inactive RAS
Activation
Active RAS
Bridging protein
Activates
GDP
GTP
Inactivation by hydrolysis of GTP
GAP
Active RAS
PTEN
RAF
PI3K
Akt
mTOR
MAPK
Pro-growth metabolism
MYC
Activation of transcription
Increased protein synthesis
D cyclins
Cell cycle progression
CELL GROWTH

# ABL-BCR hybrid gene

NORMALLY→

- ABL gene is a protooncogene having tyrosine kinase activity.

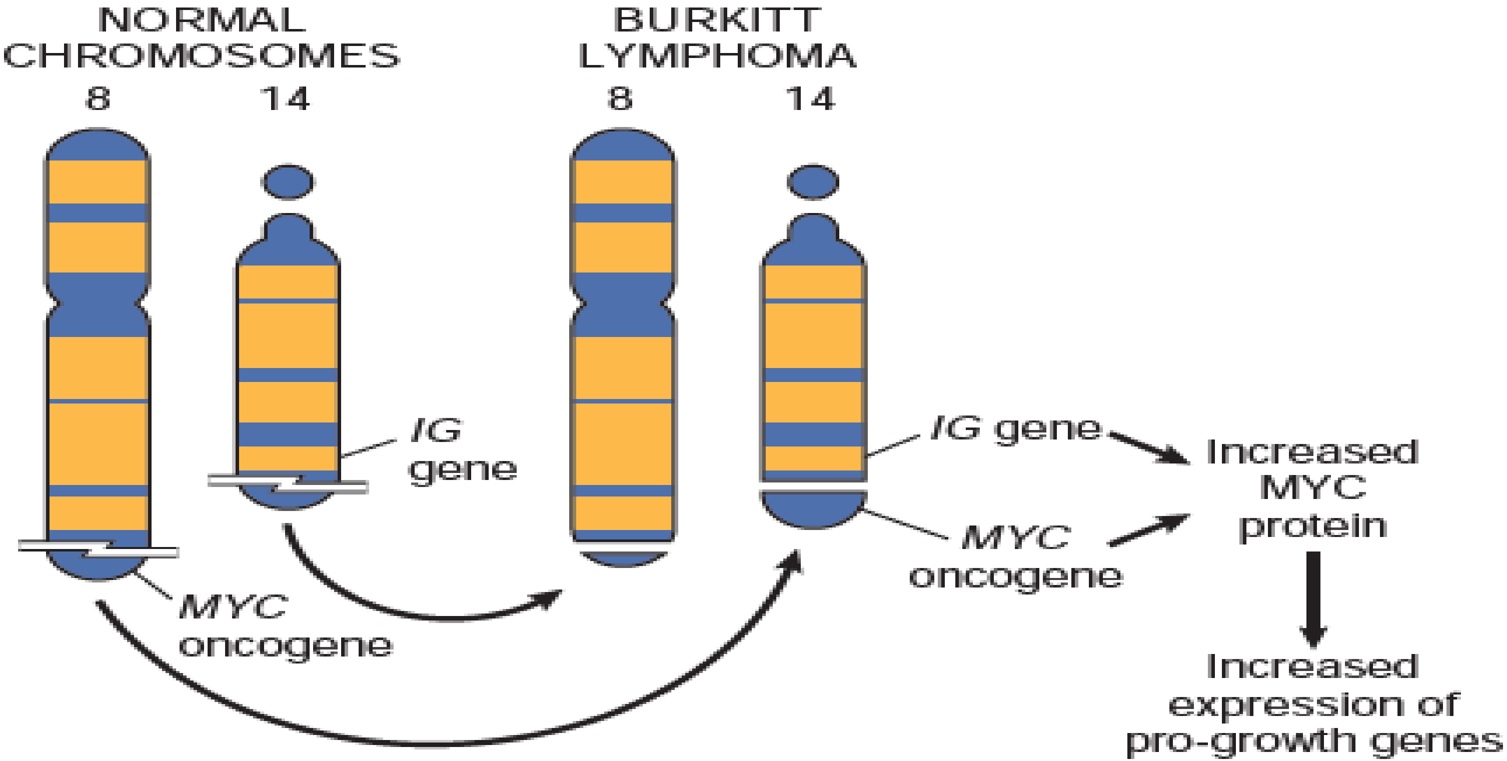
- **ABL gene** → normal location on chromosome 9
- **BCR gene**→normal location on chromosome 22


NORMAL
CML t(9;22)
Philadelphia chromosome
p arm
q arm
abl
abl
Chromosome 9
p arm
q arm
bcr
bcr
Chromosome 22
22 q
9 q
bcr
abl
bcr
abl
bcr-abl fusion gene

# MYC

- These are nuclear regulatory proteins (transcriptional activators).

- These are involved in carcinogenesis of many cancers


NORMAL CHROMOSOMES
8
14
*IG* gene
*MYC* oncogene
BURKITT LYMPHOMA
8
14
*IG* gene
*MYC* oncogene

Increased MYC protein

Increased expression of pro-growth genes

# In cancer

i) Activation of proto-oncogenes

ii) Inactivation of tumour-suppressor genes

iii) Abnormal apoptosis regulatory genes

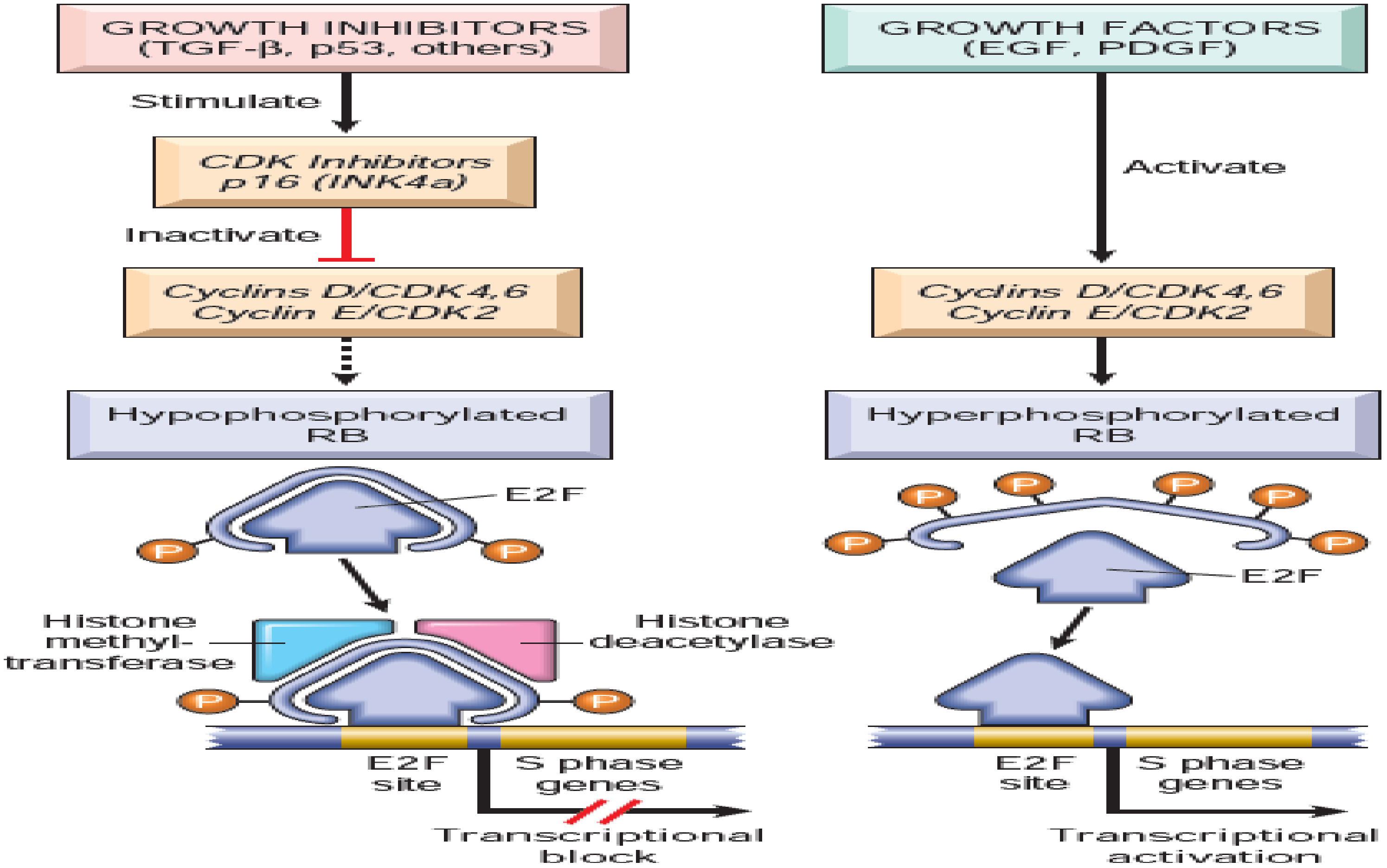
iv) Inactivation of DNA repair genes

# Tumour sppressor genes

# RB gene

- Located on long arm (q) of **chromosome 13 (chromosome 13q14)**

- RB gene was the **first tumor suppressor gene to be discovered**



GROWTH INHIBITORS (TGF-β, p53, others)

Stimulate

*CDK Inhibitors p16 (INK4a)*

Inactivate

*Cyclins D/CDK4,6 Cyclin E/CDK2*

Hypophosphorylated RB

GROWTH FACTORS (EGF, PDGF)

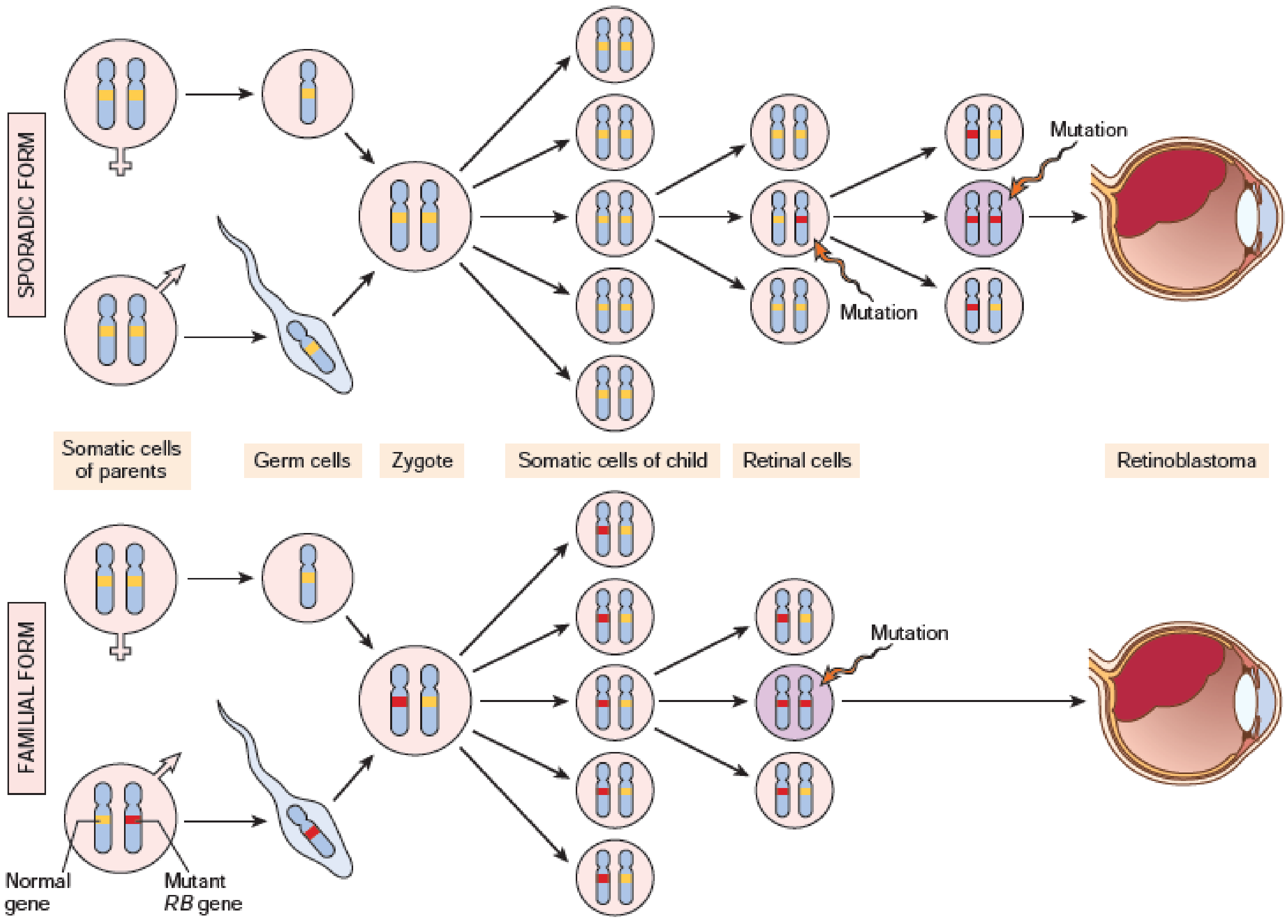
Activate

*Cyclins D/CDK4,6 Cyclin E/CDK2*

Hyperphosphorylated RB

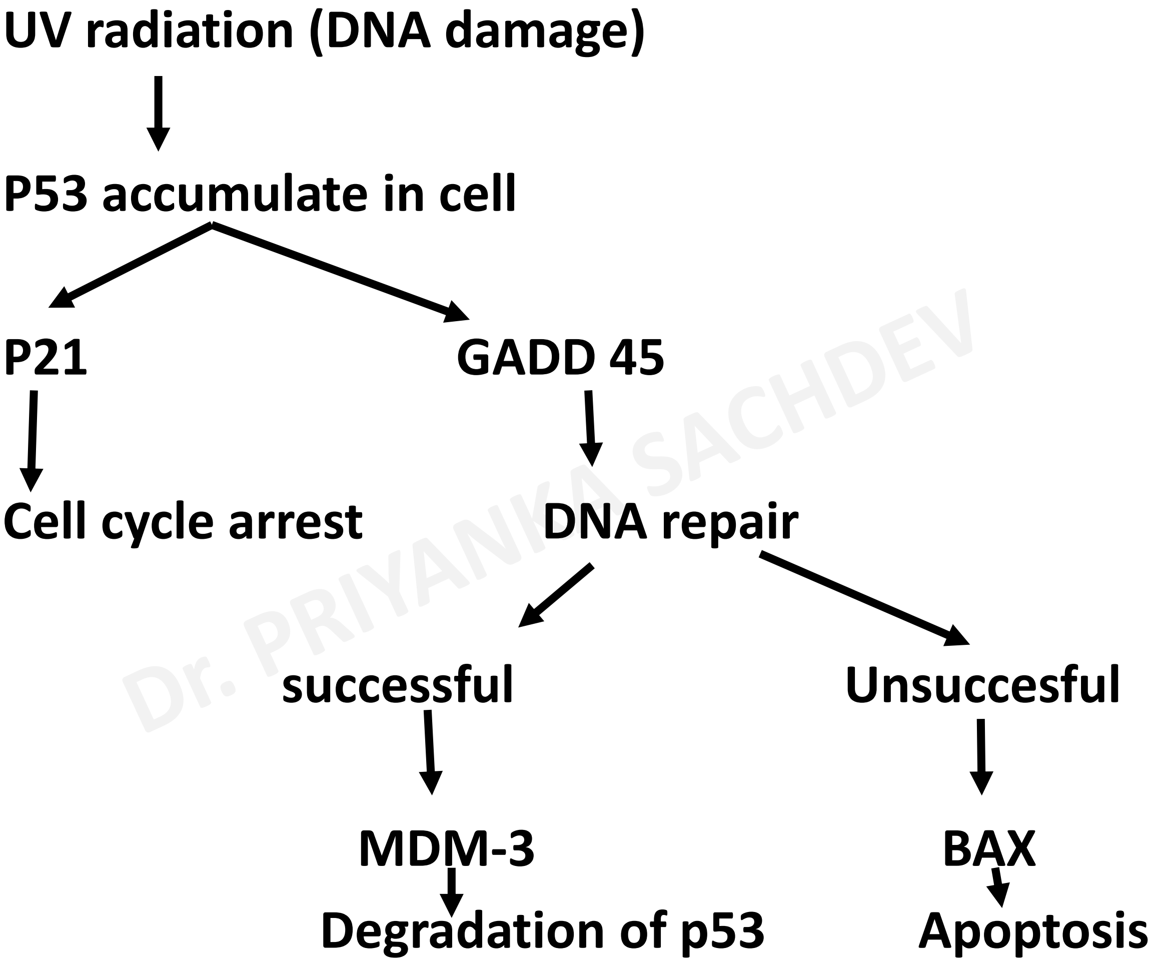
E2F
P
P
Histone methyltransferase
Histone deacetylase
P
P
E2F site
S phase genes
Transcriptional block
P
P
P
P
P
P
E2F
E2F site
S phase genes
Transcriptional activation

# PATHOGENESIS OF RETINOBLASTOMA


SPORADIC FORM
Mutation
Mutation
Somatic cells of parents
Germ cells
Zygote
Somatic cells of child
Retinal cells
Retinoblastoma
FAMILIAL FORM
Mutation
Normal gene
Mutant *RB* gene

# P53 gene

- p53 is a **tumor suppressor gene.**
- p53 gene is located on **chromosome 17**
- **Guardian of genome**
- **Molecular policeman**



UV radiation (DNA damage)

P53 accumulate in cell

P21

GADD 45

Cell cycle arrest

DNA repair

successful

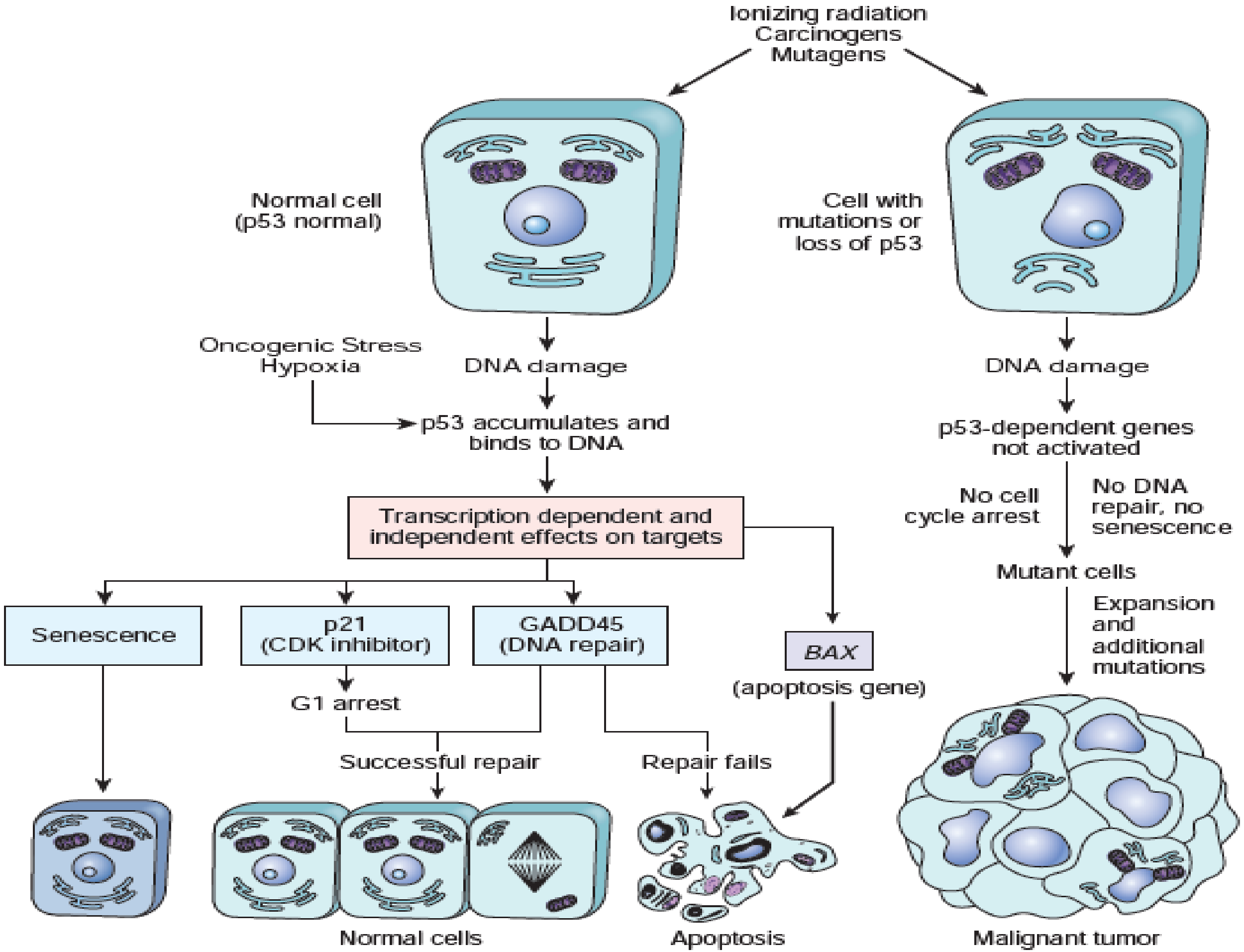
Unsuccesful

MDM-3

Degradation of p53

BAX

Apoptosis



Ionizing radiation
Carcinogens
Mutagens

Normal cell
(p53 normal)

Cell with
mutations or
loss of p53

Oncogenic Stress
Hypoxia

DNA damage

p53 accumulates and
binds to DNA

Transcription dependent and
independent effects on targets

Senescence

p21
(CDK inhibitor)

G1 arrest

GADD45
(DNA repair)

*BAX*
(apoptosis gene)

Successful repair

Repair fails

Normal cells

Apoptosis

DNA damage

p53-dependent genes
not activated

No cell
cycle arrest

No DNA
repair, no
senescence

Mutant cells

Expansion
and
additional
mutations

Malignant tumor

# In cancer

i) Activation of proto-oncogenes

ii) Inactivation of tumour-suppressor genes

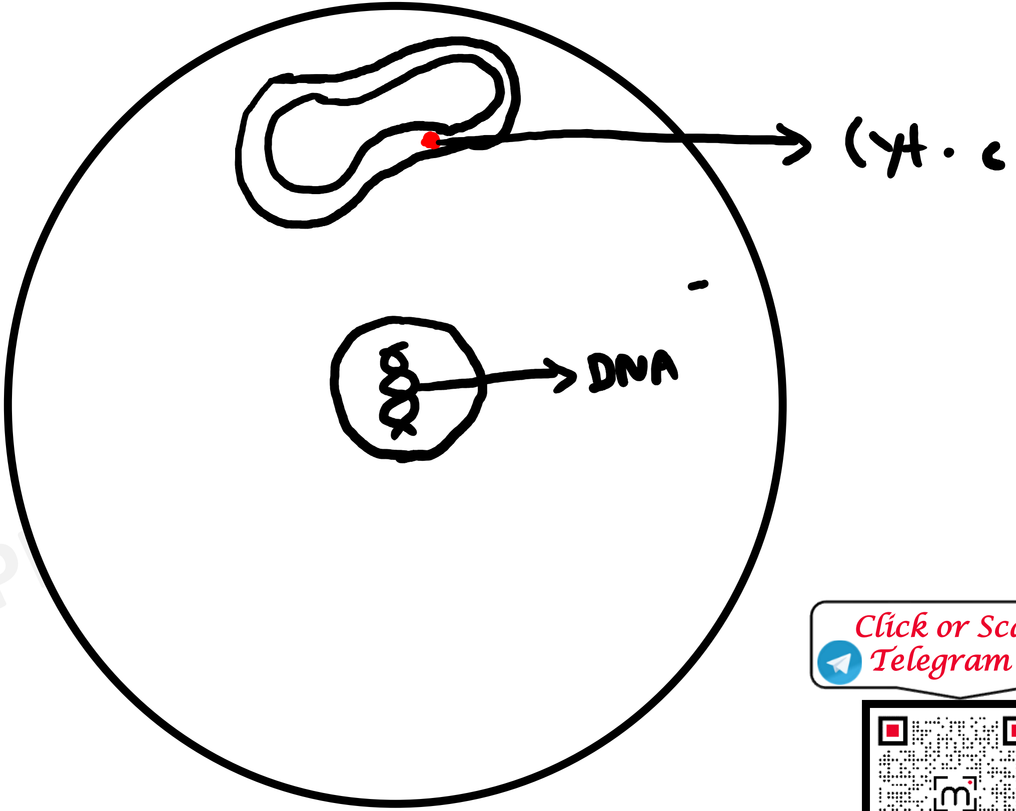
iii) Abnormal apoptosis regulatory genes

iv) Inactivation of DNA repair genes

# 3. Escaping Cell Death: Apoptosis Regulating genes

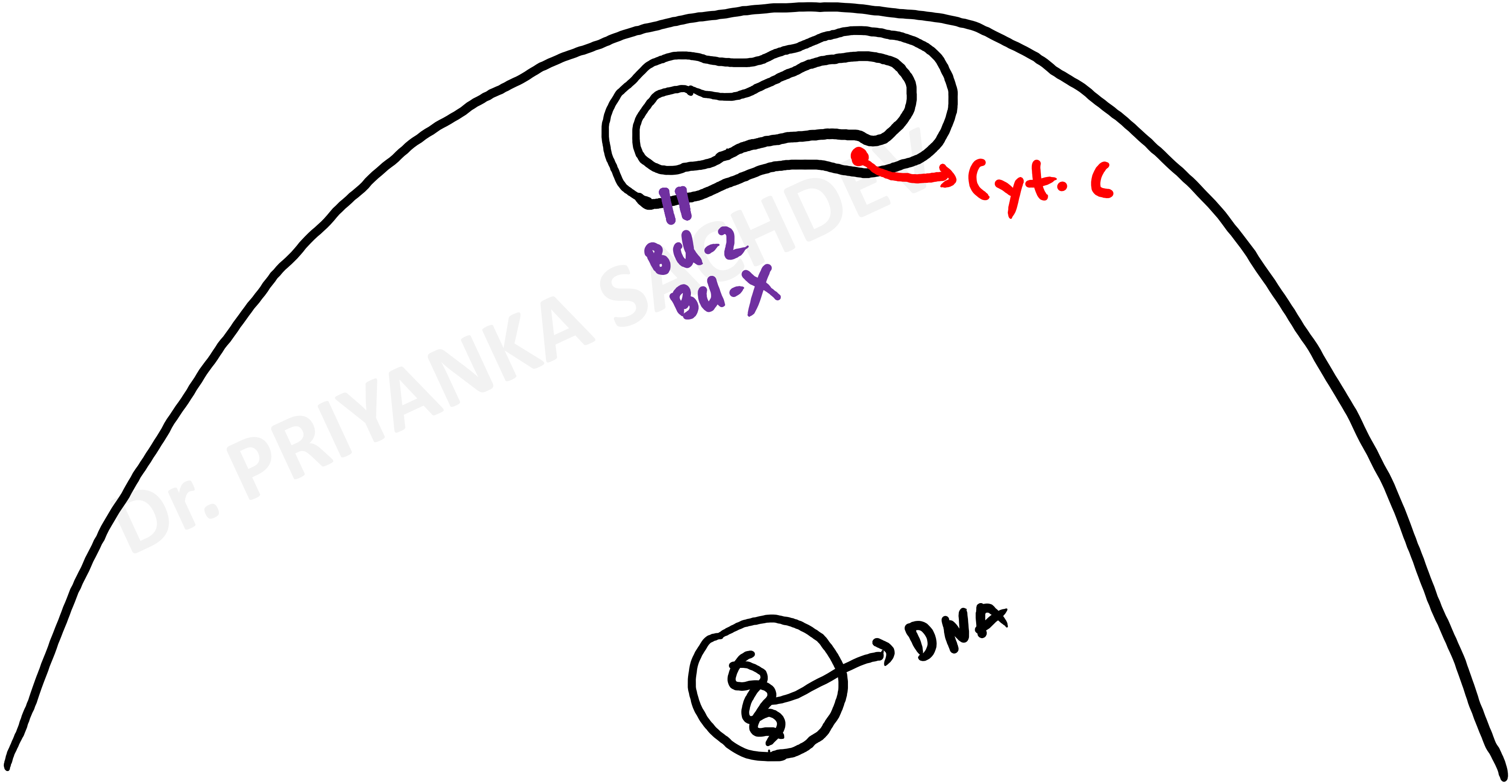
Apoptosis in **normal cell** is guided by

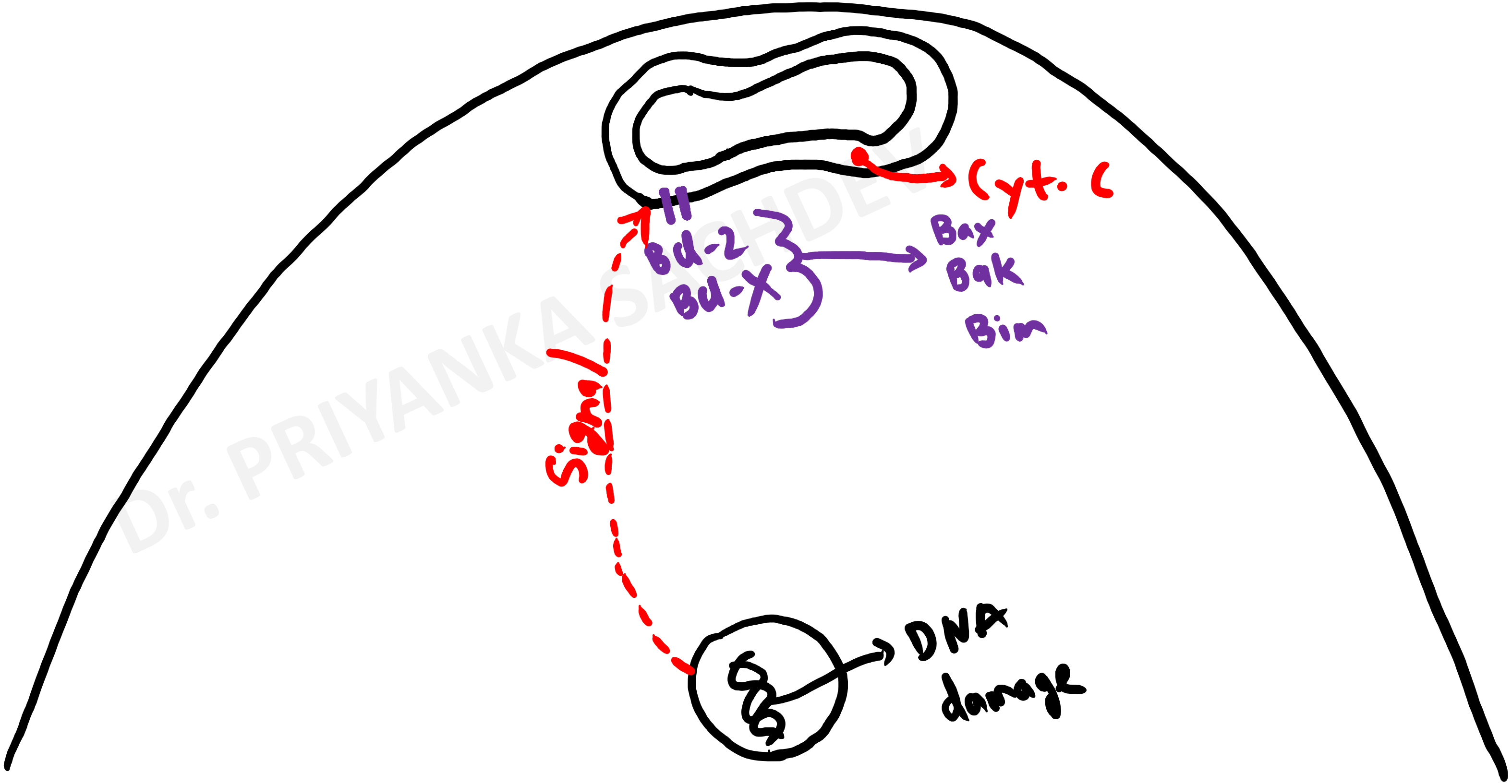
1. Pro-apoptotic factors (BAD, BAX, BID and p53)
2. Anti apoptosis factors (BCL2, BCL-X).

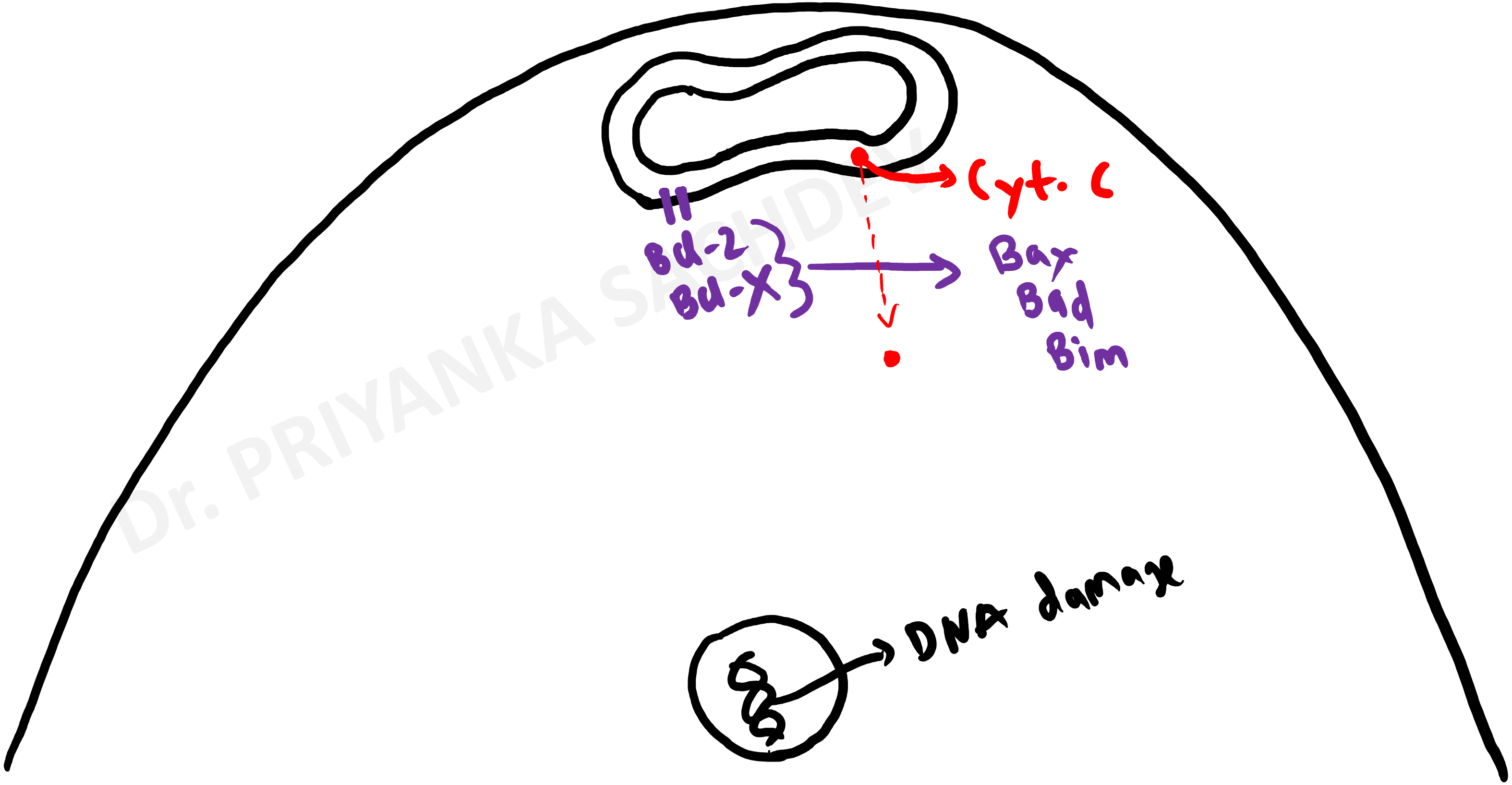


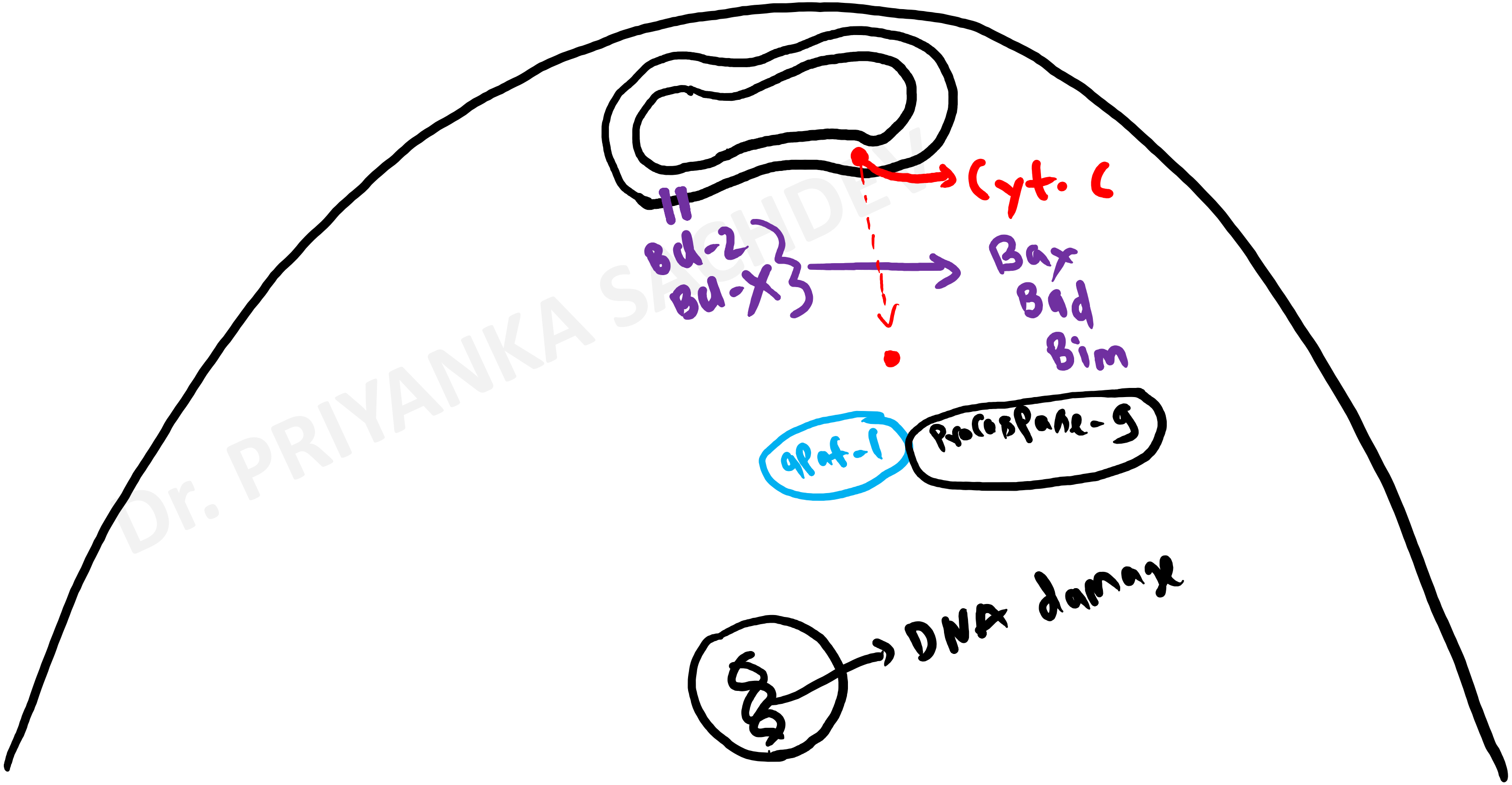
Dr. P

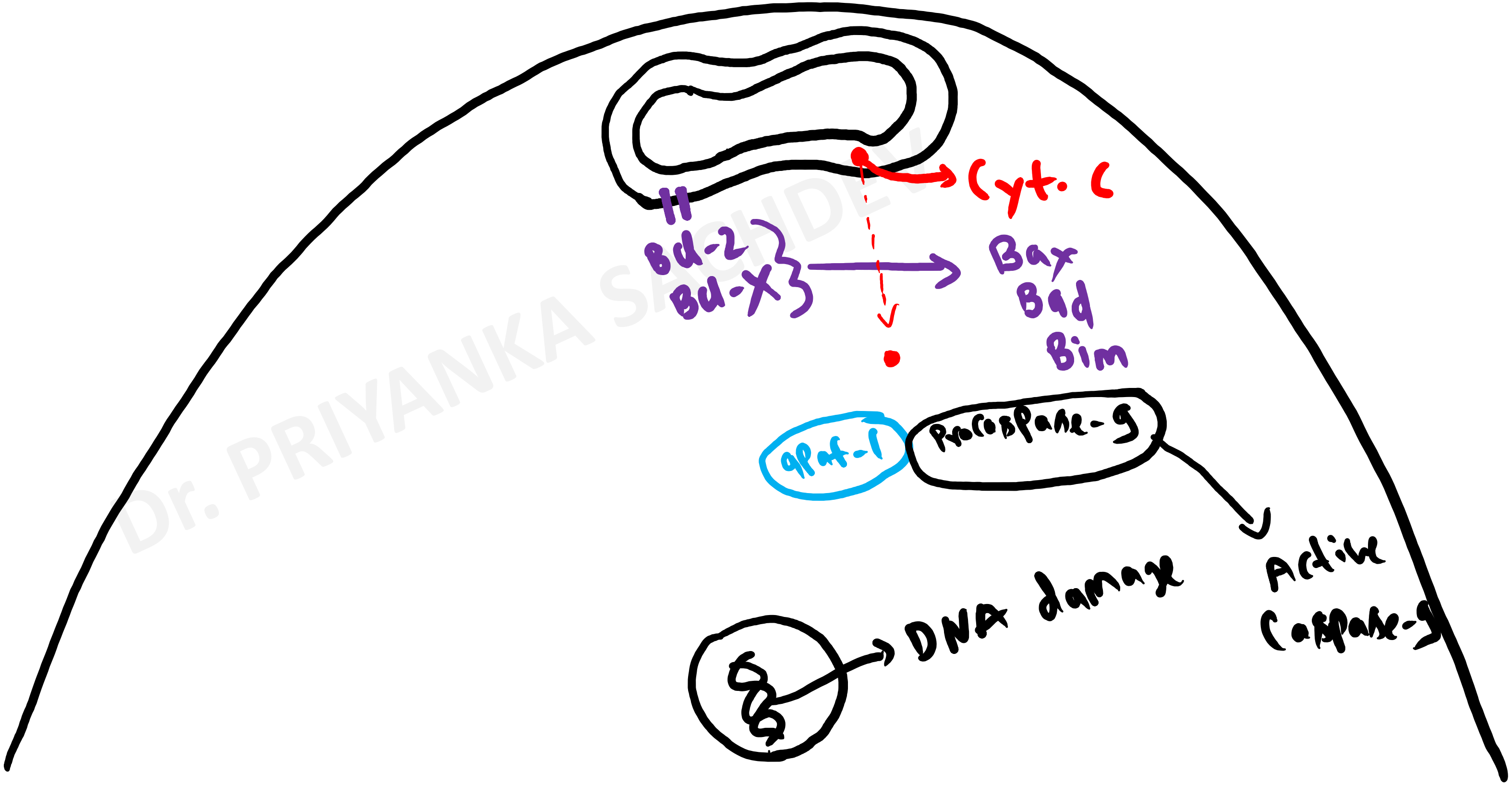
Click or Scan QR code to join
Telegram group discussion

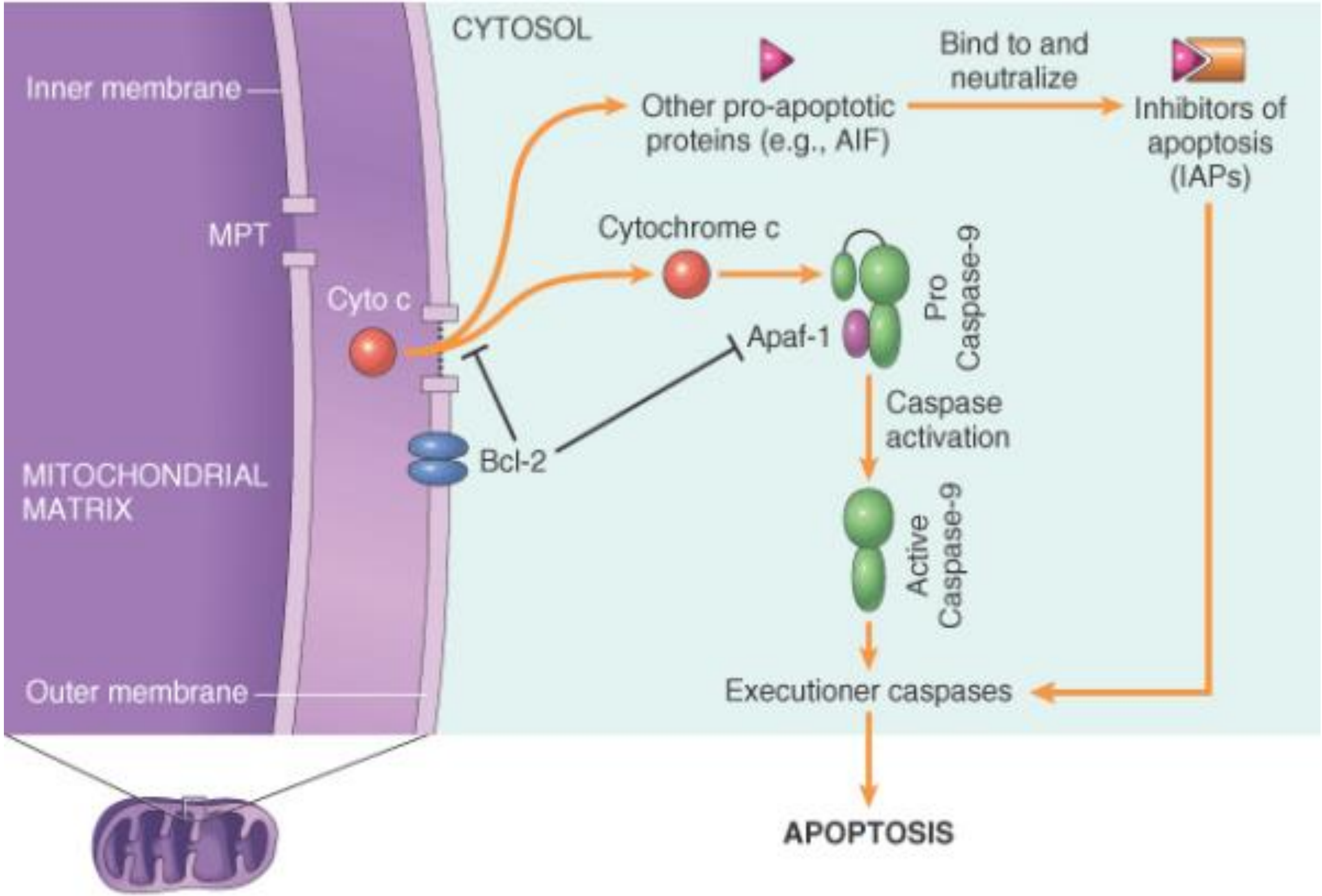

Bcl-2
Bcl-X
Cyt. C
DNA


Cyt. C
Bcl-2
Bcl-X
Bax
Bak
Bim
Signal
DNA damage

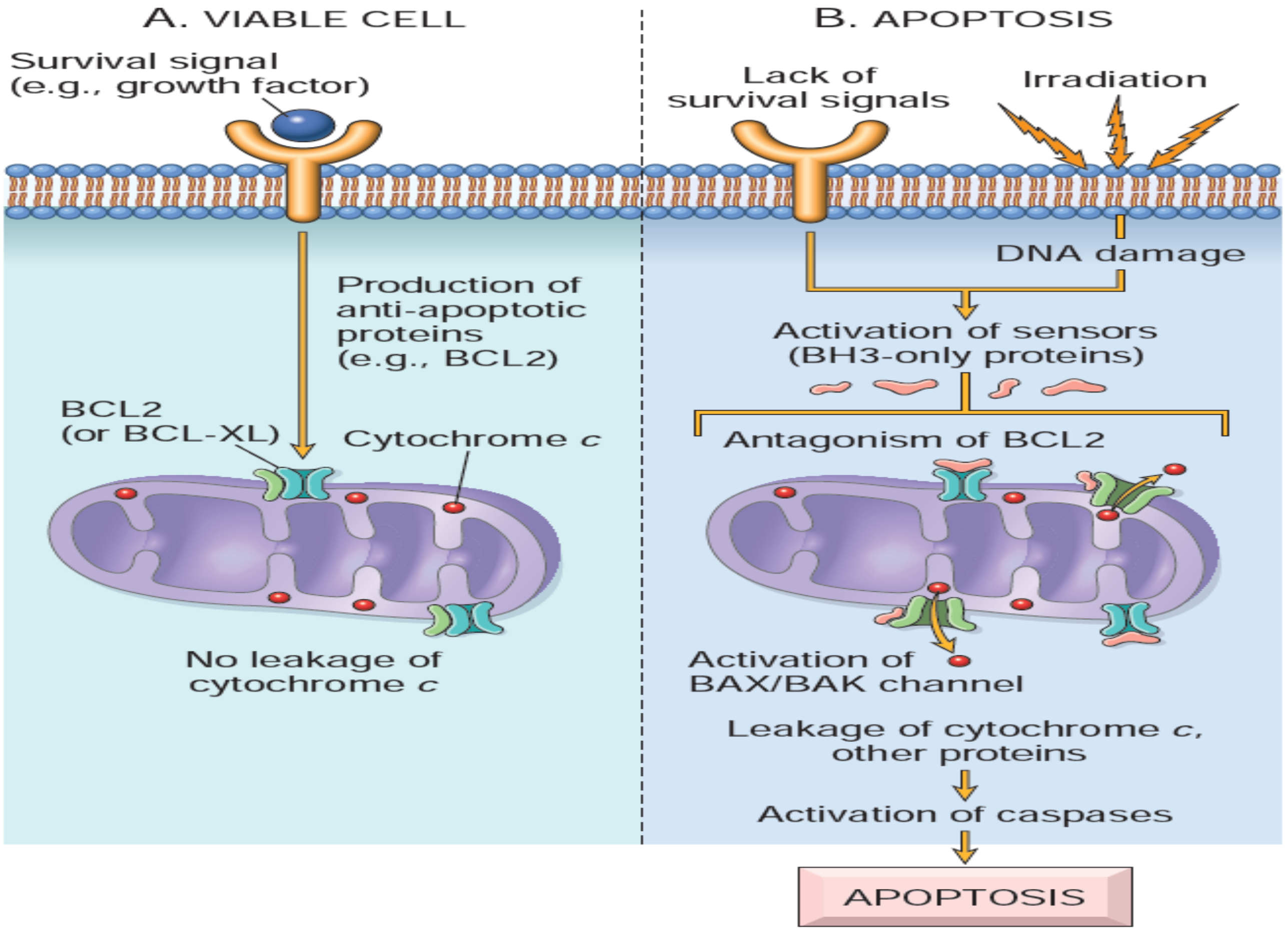

Cyt. c
Bcl-2
Bcl-X
Bax
Bad
Bim
DNA damage


Cyt. C
Bcl-2
Bcl-X
Bax
Bad
Bim
Apaf-1
Procaspase-9
DNA damage


Cyt. c
Bcl-2
Bcl-X
Bax
Bad
Bim
Apaf-1
Procaspase-9
Active Caspase-9
DNA damage


CYTOSOL
Inner membrane
MPT
Cyto c
MITOCHONDRIAL MATRIX
Outer membrane
Bcl-2
Other pro-apoptotic proteins (e.g., AIF)
Bind to and neutralize
Inhibitors of apoptosis (IAPs)
Cytochrome c
Apaf-1
Pro Caspase-9
Caspase activation
Active Caspase-9
Executioner caspases
APOPTOSIS

**Dr. PRIYANKA SACHDEV**



A. VIABLE CELL

Survival signal (e.g., growth factor)

Production of anti-apoptotic proteins (e.g., BCL2)

BCL2 (or BCL-XL)

Cytochrome *c*

No leakage of cytochrome *c*

B. APOPTOSIS

Lack of survival signals

Irradiation

DNA damage

Activation of sensors (BH3-only proteins)

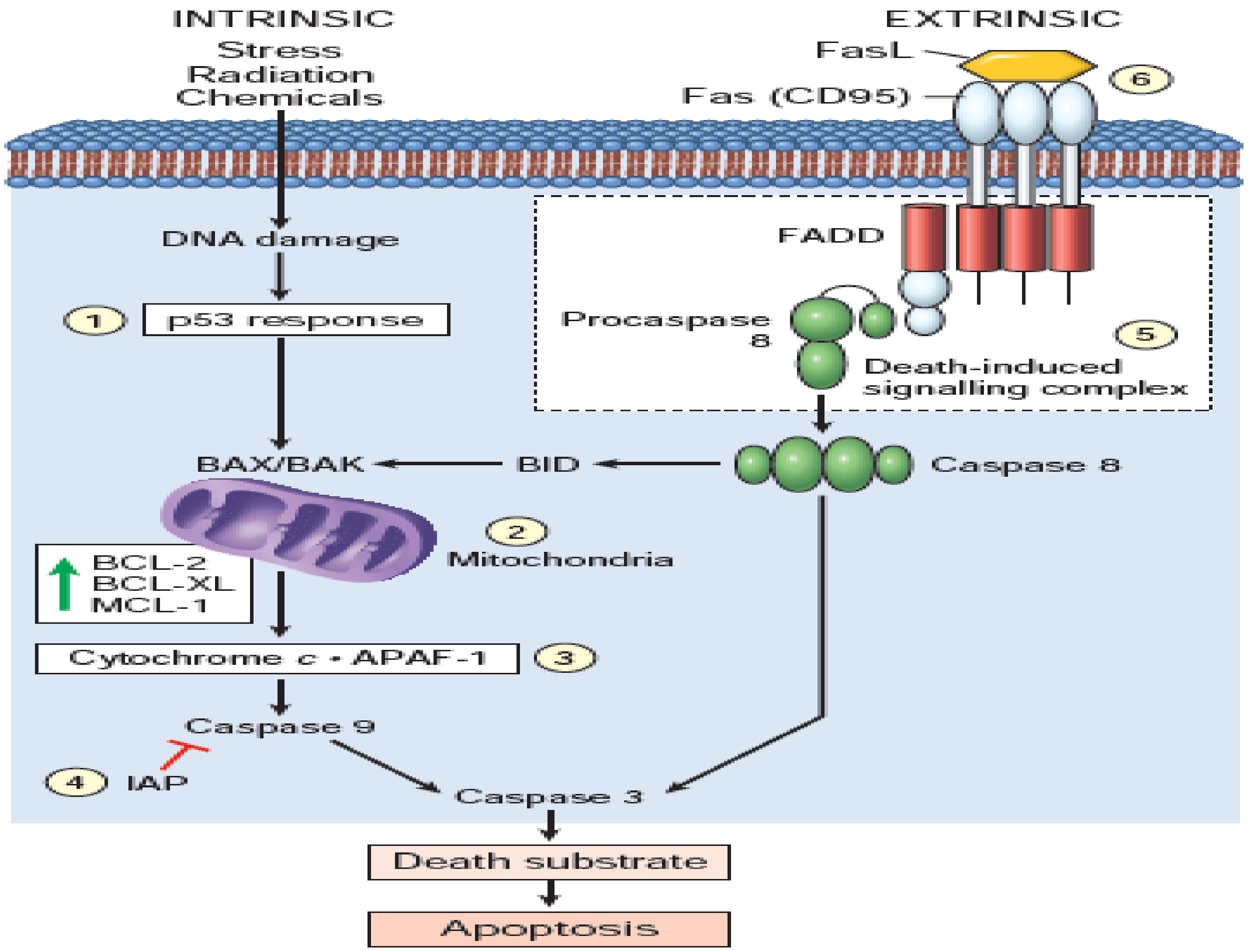
Antagonism of BCL2

Activation of BAX/BAK channel

Leakage of cytochrome *c*, other proteins

Activation of caspases

APOPTOSIS



INTRINSIC
Stress
Radiation
Chemicals
EXTRINSIC
FasL
Fas (CD95)
6
DNA damage
1
p53 response
FADD
Procaspase 8
5
Death-induced signalling complex
BAX/BAK
BID
Caspase 8
2
Mitochondria
BCL-2
BCL-XL
MCL-1
Cytochrome *c* • APAF-1
3
Caspase 9
4
IAP
Caspase 3
Death substrate
Apoptosis

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In **cancer cells**, the function of apoptosis is interfered due to mutations in the above genes which regulate apoptosis in the normal cell.

Mutation in apoptosis Regulating genes

↓

1. Inactivation of proapoptotic factors(BAD, BAX, BID and p53)
2. Overactivation of antiapoptotic factors(BCL2, BCL-X)

↓

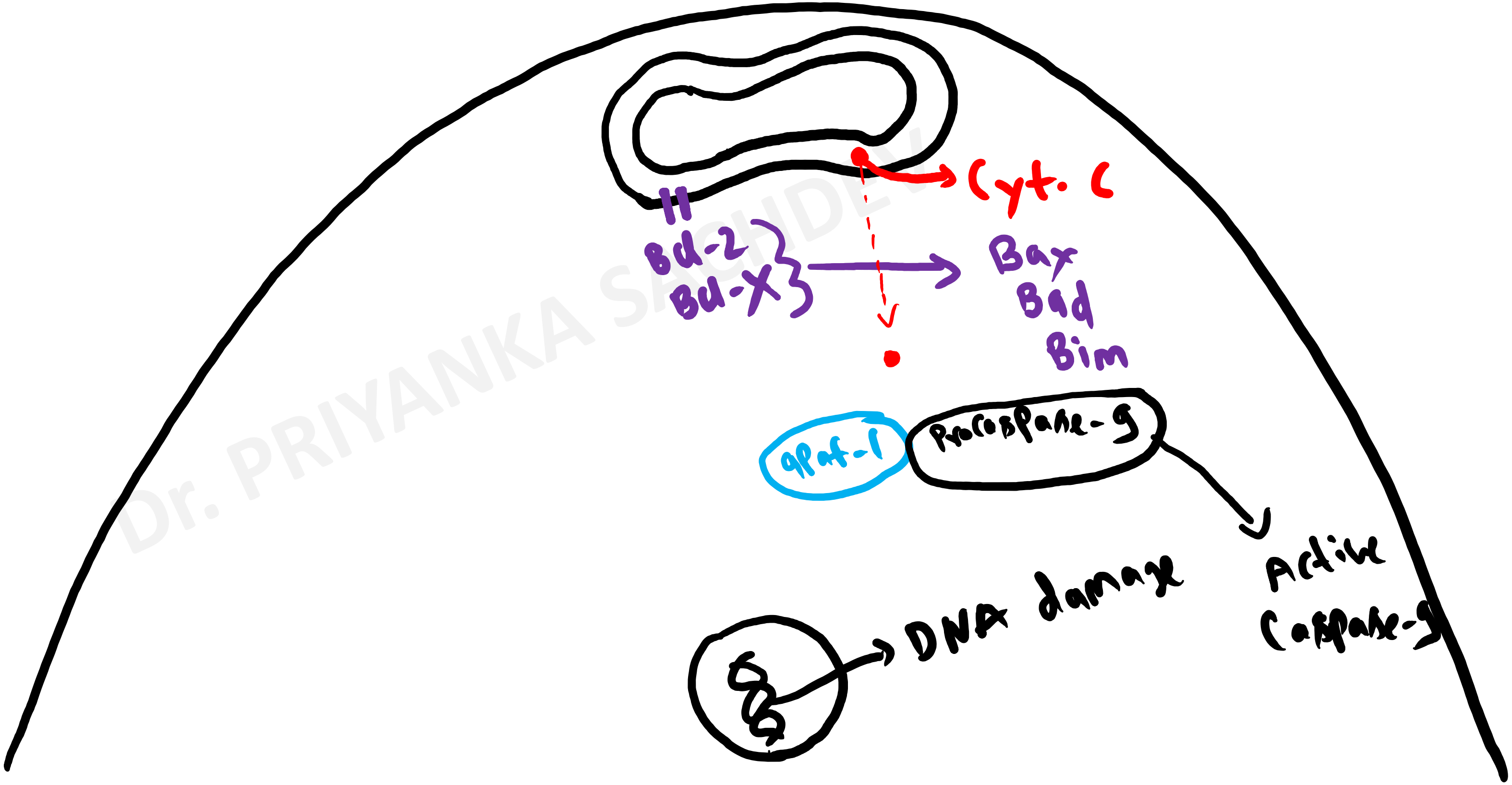
Escaping Cell Death

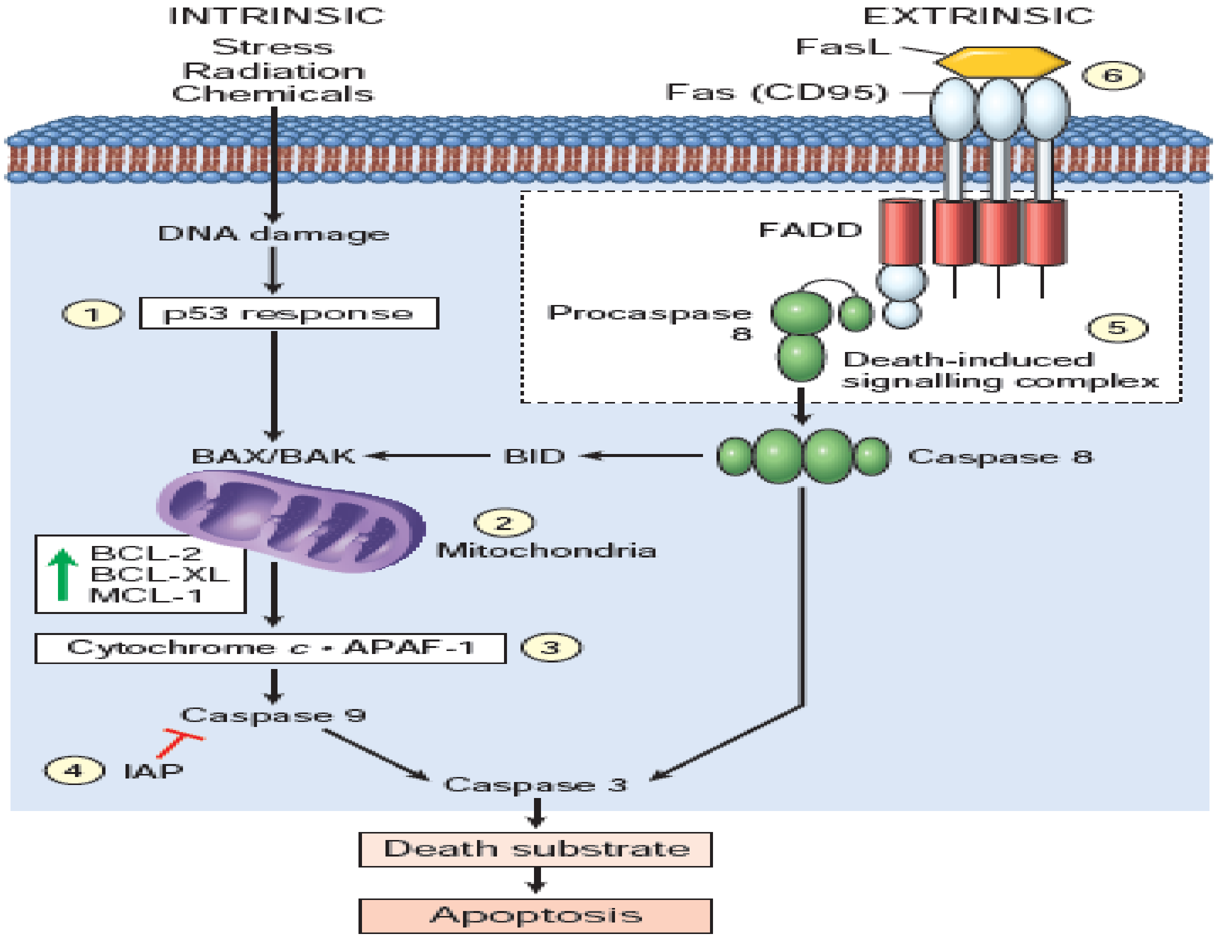
↓

Uncontrolled growth

↓

Cancer


Cyt. C
||
Bcl-2
Bcl-X
Bax
Bad
Bim
Apaf-1
Procaspase-9
Active Caspase-9
DNA damage


INTRINSIC
Stress
Radiation
Chemicals
EXTRINSIC
FasL
6
Fas (CD95)
FADD
DNA damage
1
p53 response
Procaspase 8
5
Death-induced signalling complex
BAX/BAK
BID
Caspase 8
2
Mitochondria
BCL-2
BCL-XL
MCL-1
Cytochrome c • APAF-1
3
Caspase 9
4
IAP
Caspase 3
Death substrate
Apoptosis

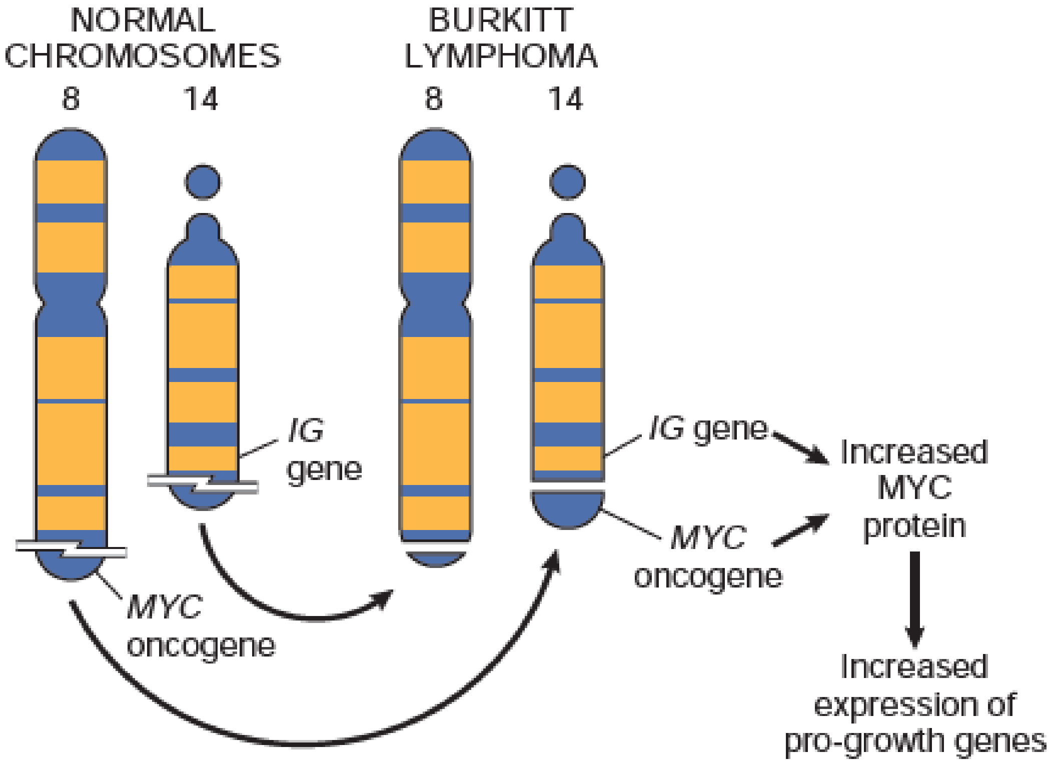
**Dr. PRIYANKA SACHDEV**

- Of these two pathways, it is the **intrinsic apoptotic pathway** (sometimes referred to as the mitochondrial pathway) that is most frequently disabled in cancer.

# Eg.

Normally

- chromosome 14 has **immunoglobulin heavy chain gene**
- Chromosome 18 has **bcl-2 gene.**



NORMAL CHROMOSOMES
8
14
IG gene
MYC oncogene
BURKITT LYMPHOMA
8
14
IG gene
MYC oncogene
Increased MYC protein
Increased expression of pro-growth genes

**Dr. PRIYANKA SACHDEV**

In **follicular lymphoma**

↓

there is presence of translocation **t (14:18)**

↓

which causes increased expression of bcl-2

↓

thereby preventing apoptosis

↓

protects lymphocytes from apoptosis and contributes to the survival of transformed B cells.

↓

Inducing the development of cancer.

# In cancer

i) Activation of proto-oncogenes

ii) Inactivation of tumour-suppressor genes

iii) Abnormal apoptosis regulatory genes

iv) Inactivation of DNA repair genes

# 4. DNA Damage and Repair System

- DNA damage by exogenous factors (e.g. by radiation, chemical carcinogens etc) or during mitosis is repaired.

- **p53** gene is held responsible for detection and repair of DNA damage

**DNA damage**

↓

**If this system of DNA repair is defective**

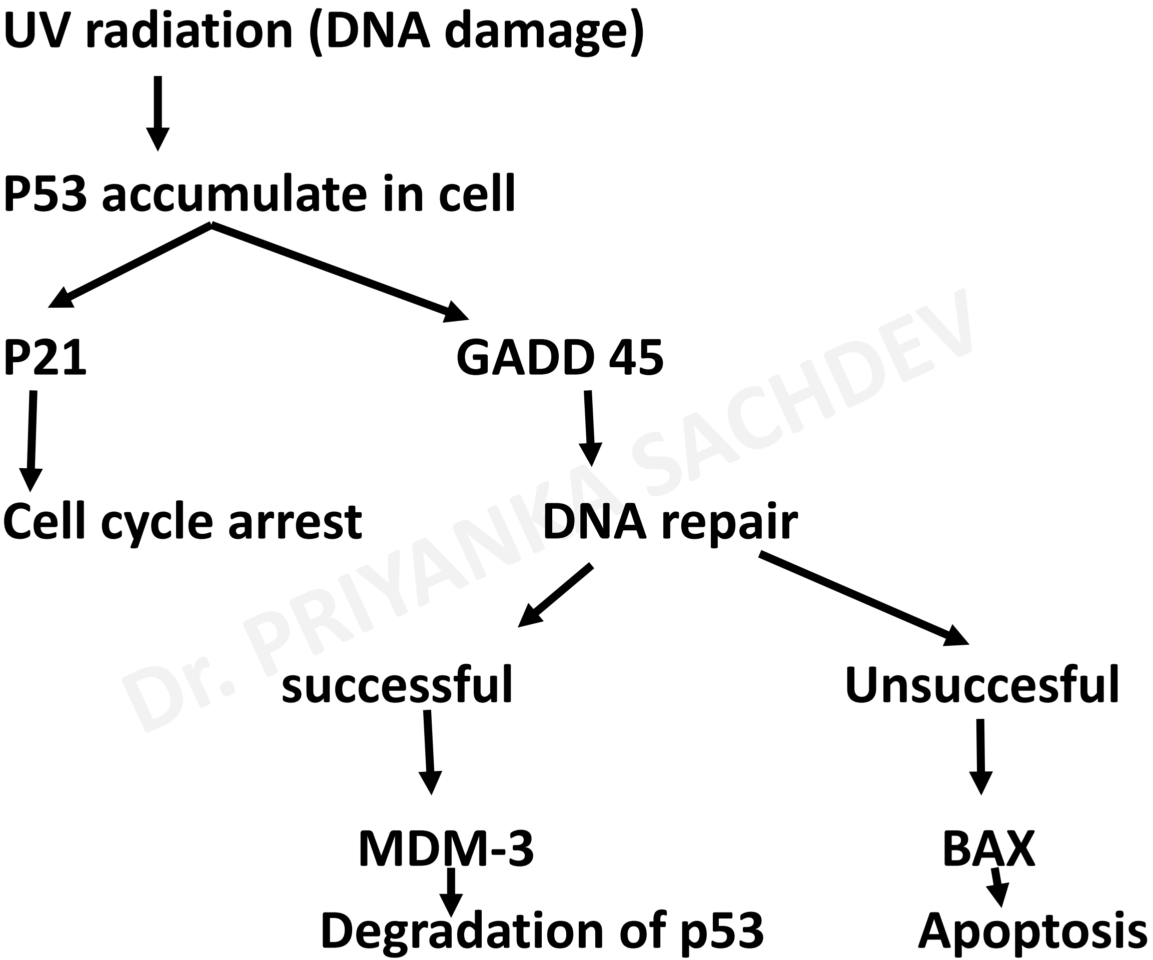
↓

**The defect in unrepaired DNA is passed to the next progeny of cells**

↓

**cancer results**

# NORMALLY p53



UV radiation (DNA damage)

P53 accumulate in cell

P21

GADD 45

Cell cycle arrest

DNA repair

successful

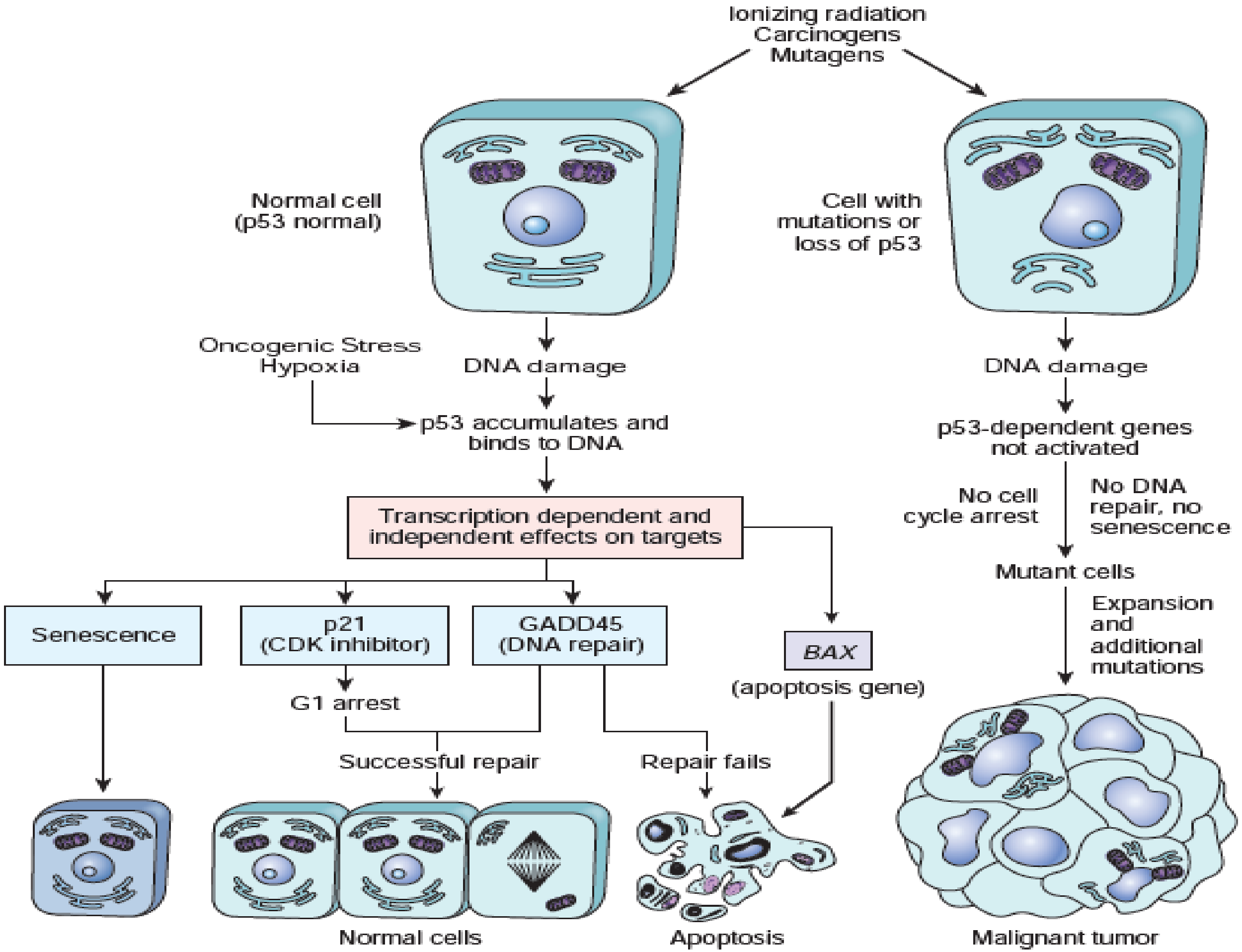
Unsuccesful

MDM-3

BAX

Degradation of p53

Apoptosis



Ionizing radiation
Carcinogens
Mutagens

Normal cell
(p53 normal)

Cell with
mutations or
loss of p53

Oncogenic Stress
Hypoxia

DNA damage

p53 accumulates and
binds to DNA

Transcription dependent and
independent effects on targets

Senescence

p21
(CDK inhibitor)

G1 arrest

GADD45
(DNA repair)

*BAX*
(apoptosis gene)

Successful repair

Repair fails

Normal cells

Apoptosis

DNA damage

p53-dependent genes
not activated

No cell
cycle arrest

No DNA
repair, no
senescence

Mutant cells

Expansion
and
additional
mutations

Malignant tumor

**Dr. PRIYANKA SACHDEV**

# REMEMBER

- The cell cycle has its own internal controls, called **checkpoints**. There are two main checkpoints, one at the **G1/S transition and another at G2/M.**

- In the **G1/S checkpoint**, **cell-cycle arrest is mostly mediated through p53**, which induces the cell-cycle inhibitor p21.

- Arrest of the cell cycle by the **G2/M checkpoint** involves **both p53-dependent (via cyclin A/cdK-2) and independent (via cdc 25)** mechanisms

# Mutation in p53

**Cells with mutation or loss of p53**

↓

**DNA damage**

↓

**p53 dependent genes not activated**

↓

**No cell cycle arrest**

**No DNA repair**

↓

**Mutant cells→Expansion and additional mutations**

↓

**Cancer**

Eg

- i) Hereditary non-polyposis colon cancer (HNPCC or Lynch syndrome)
- ii) Ataxia telangiectasia (AT)
- iii) Xeroderma pigmentosum
- iv) Bloom syndrome.
- V) Fanconi anemia

# Fanconi's anemia

- Fanconi's anemia is an **autosomal recessive** disease characterized by

1. progressive **pancytopenia**
2. increased risk of malignancy **(solid tumors and AML)**
3. congenital developmental anomalies like short stature, café au lait spots, abnormalities affecting thumb, radius and genitourinary tract.

- Fanconi's anemia is associated with **BRCA gene.**
- The Fanconi anemia proteins and BRCA proteins form a **DNA-damage repair proteins** to correct intrastrand and interstrand DNA cross links induced by chemical cross-linking agents.

- **Hereditary non polyposis colon cancer (HNPCC)** is an **autosomal dominant** condition caused by *defective DNA repair* genes.

- **All others** are conditions associated with defective DNA repair genes are **autosomal recessive**

## Defects in DNA repair

- Nucleotide excision repair
  - Xeroderma pigmentosum$^{Q}$
- Mismatch repair
  - Hereditary non-polyposis colorectal carcinoma syndrome$^{Q}$
- Recombination repair
  - Bloom syndrome$^{Q}$
  - Ataxia telangiectasia$^{Q}$
  - Fanconi's anemia$^{Q}$

# In cancer

i) Activation of proto-oncogenes

ii) Inactivation of tumour-suppressor genes

iii) Abnormal apoptosis regulatory genes

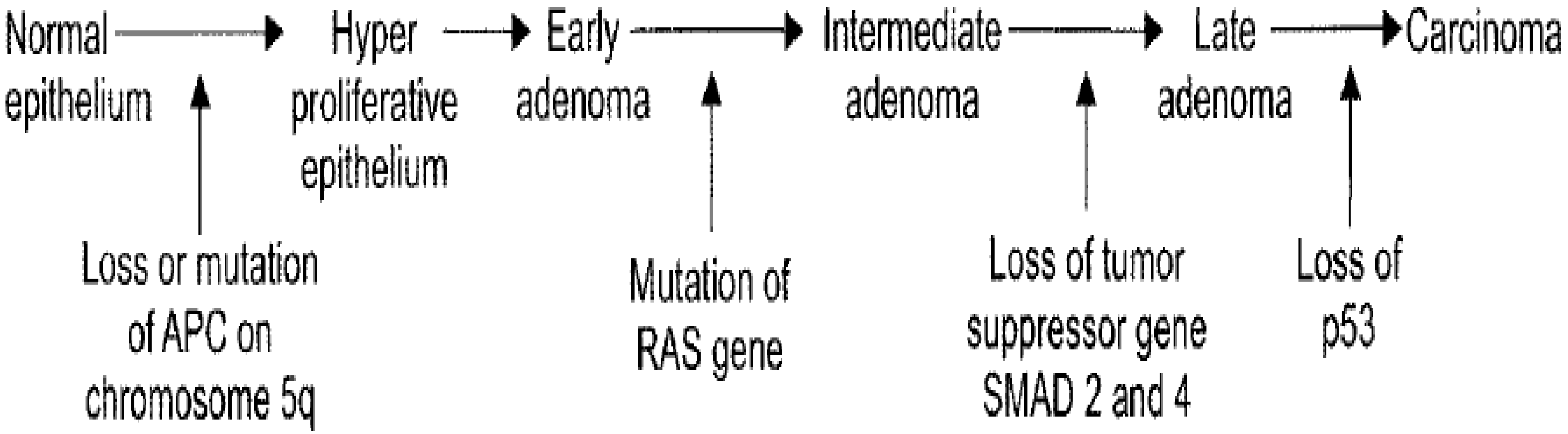
iv) Inactivation of DNA repair genes

# Cancer: Multistep Theory

Multiple steps :

- Activation of Proto oncogenes
- Loss of tumour suppressor genes
- Inactivation of apoptotic mechanisms
- Escaping cellular ageing

- A classic example →**adenoma-carcinoma sequence in colorectal carcinoma**



Normal epithelium → Hyper proliferative epithelium → Early adenoma → Intermediate adenoma → Late adenoma → Carcinoma

Loss or mutation of APC on chromosome 5q

Mutation of RAS gene

Loss of tumor suppressor gene SMAD 2 and 4

Loss of p53

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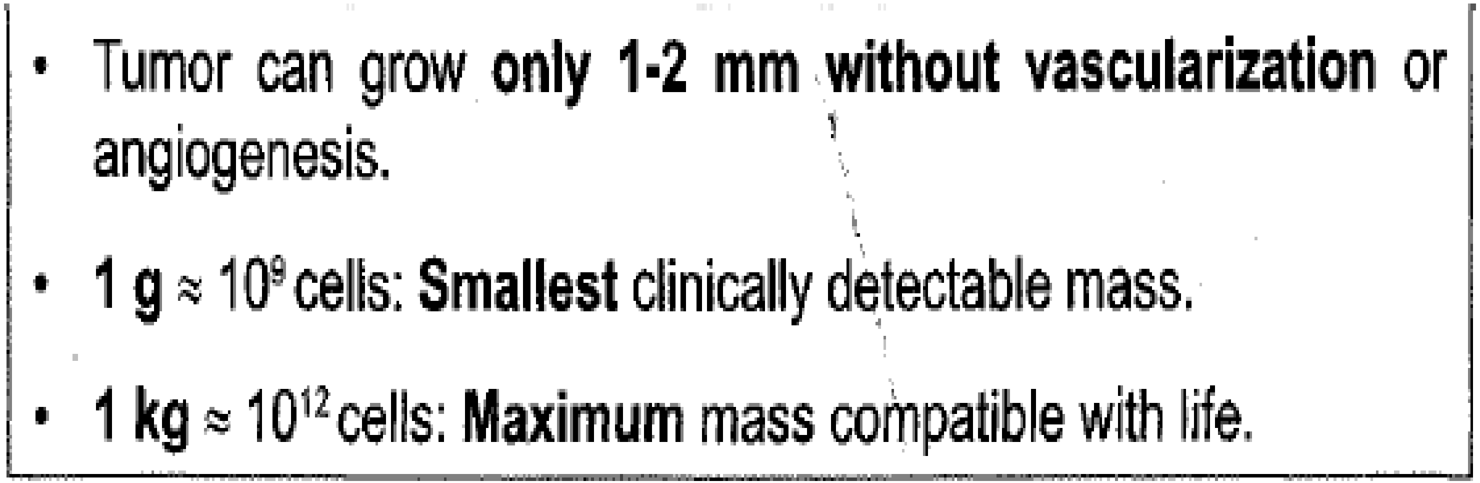
# REMEMBER

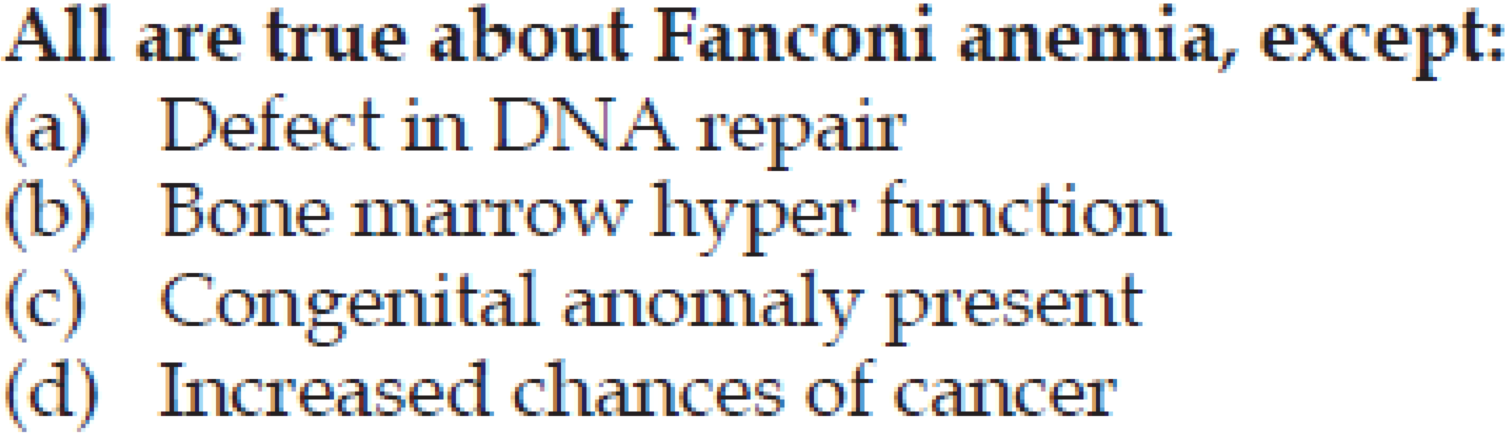


- Tumor can grow **only 1-2 mm without vascularization** or angiogenesis.
- **1 g** ≈ $10^9$ cells: **Smallest** clinically detectable mass.
- **1 kg** ≈ $10^{12}$ cells: **Maximum** mass compatible with life.

# POLLS.

Scan or Click to watch
Neoplasia E01

Scan or Click to watch
Neoplasia E02



**All are true about Fanconi anemia, except:**

(a) Defect in DNA repair
(b) Bone marrow hyper function
(c) Congenital anomaly present
(d) Increased chances of cancer

# B

**Regarding Fanconi anemia, the wrong statement is:**

(a) Autosomal dominant
(b) Bone marrow show pancytopenia
(c) Usually aplastic anemia
(d) It is due to defective DNA repair

# A

**True statements about p53 gene are all except:**

(a) Arrests cell cycle at $G_1$ phase
(b) Product is 53 kD protein
(c) Located on chromosome 17
(d) Wild/non-mutated form is associated with increased risk of childhood tumors

Dr. PRIYAN

# D

**Xeroderma pigmentosum is caused due to a group of closely related abnormalities in:**

(a) Mismatch repair
(b) Base excision repair
(c) Nucleotide excision repair
(d) SOS repair

Dr. PRIYANK

# c

Defects in DNA repair

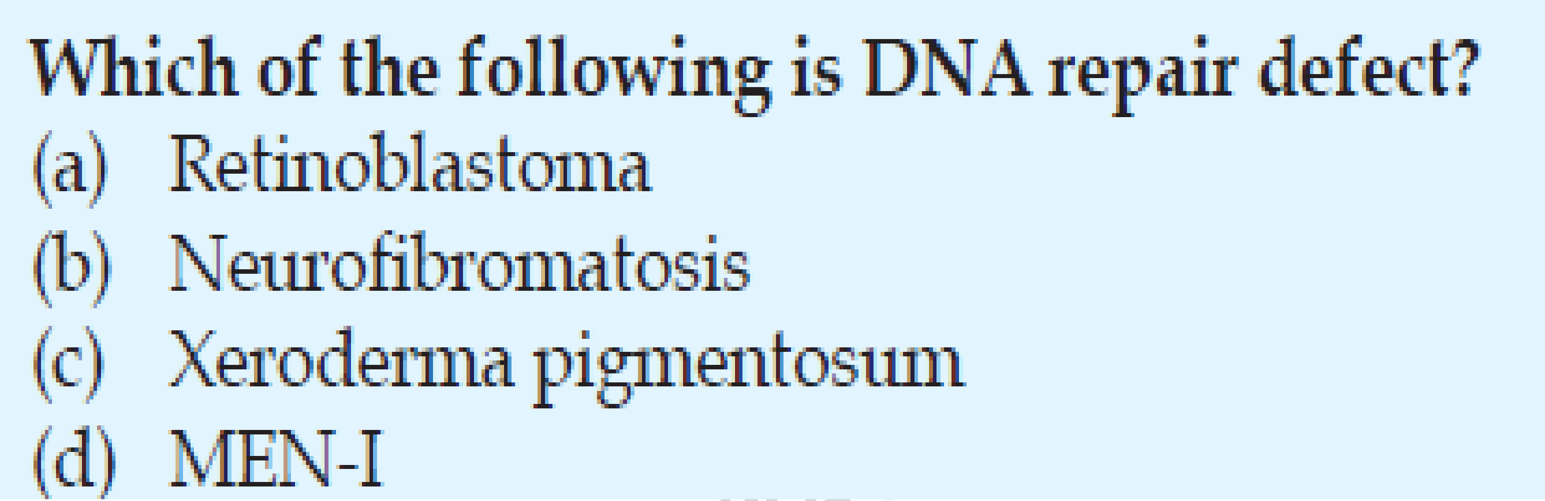
- Nucleotide excision repair
  - Xeroderma pigmentosum$^{Q}$
- Mismatch repair
  - Hereditary non-polyposis colorectal carcinoma syndrome$^{Q}$
- Recombination repair
  - Bloom syndrome$^{Q}$
  - Ataxia telangiectasia$^{Q}$
  - Fanconi's anemia$^{Q}$

**The tumor suppressor gene p 53 induces cell cycle arrest at:**

(a) G2 – M phase (b) S – G2 phase

(c) G1 – S phase (d) G0 phase

# c



**Which of the following is DNA repair defect?**

(a) Retinoblastoma
(b) Neurofibromatosis
(c) Xeroderma pigmentosum
(d) MEN-I

# c

Defects in DNA repair

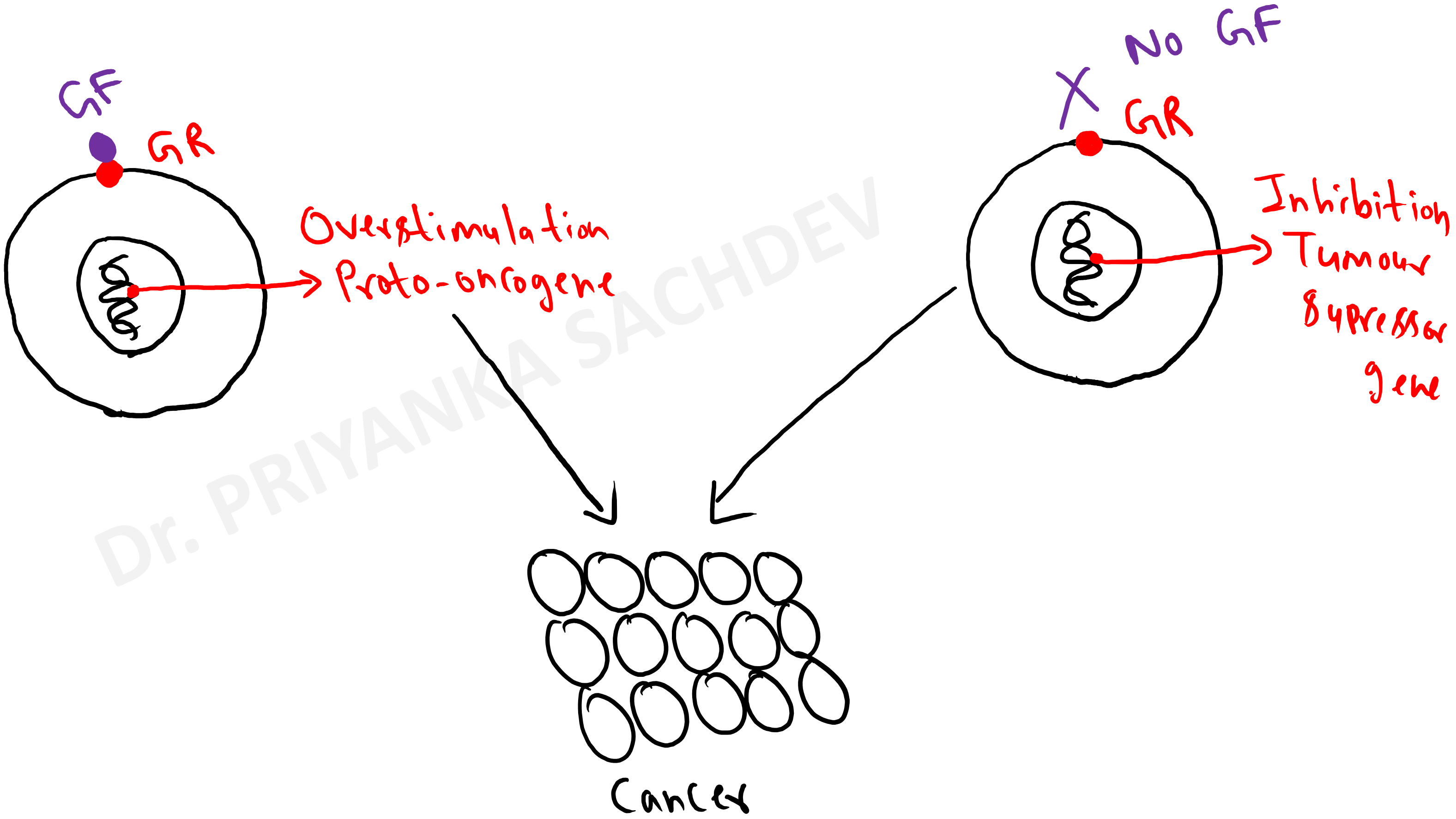
- Nucleotide excision repair
  - Xeroderma pigmentosum$^Q$
- Mismatch repair
  - Hereditary non-polyposis colorectal carcinoma syndrome$^Q$
- Recombination repair
  - Bloom syndrome$^Q$
  - Ataxia telangiectasia$^Q$
  - Fanconi's anemia$^Q$

# CARCINOGENS AND CARCINOGENESIS

- **Carcinogenesis** means mechanism of induction of tumours

- Agents which can induce tumours are called **carcinogens**

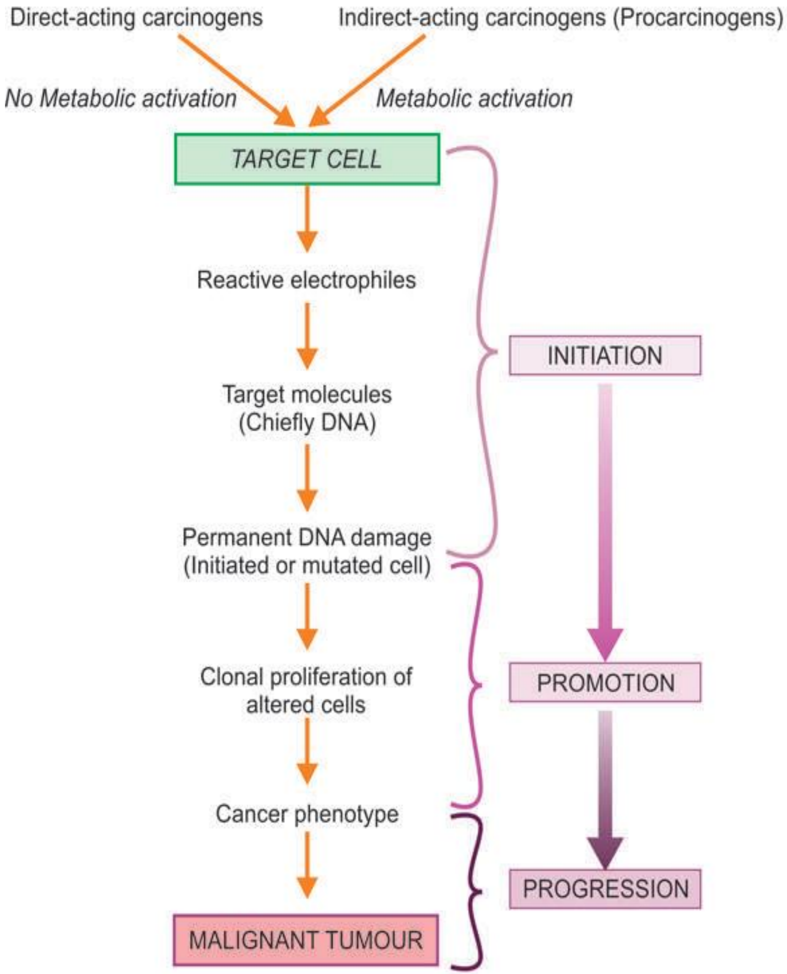
# NORMAL CELL


GF
GR
Overstimulation
Proto-oncogene
X No GF
GR
Inhibition
Tumour
Supressor
gene
Cancer

# 3 TYPES→

A. Chemical carcinogens
B. Physical carcinogens
C. Biologic carcinogens

# A. CHEMICAL CARCINOGENESIS



Direct-acting carcinogens

Indirect-acting carcinogens (Procarcinogens)

*No Metabolic activation*

*Metabolic activation*

*TARGET CELL*

Reactive electrophiles

Target molecules
(Chiefly DNA)

Permanent DNA damage
(Initiated or mutated cell)

Clonal proliferation of
altered cells

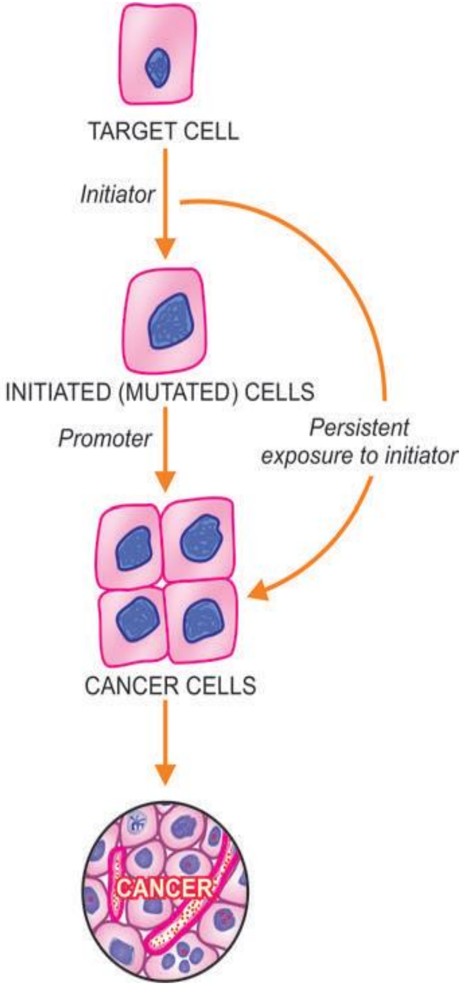
Cancer phenotype

MALIGNANT TUMOUR

INITIATION

PROMOTION

PROGRESSION



TARGET CELL

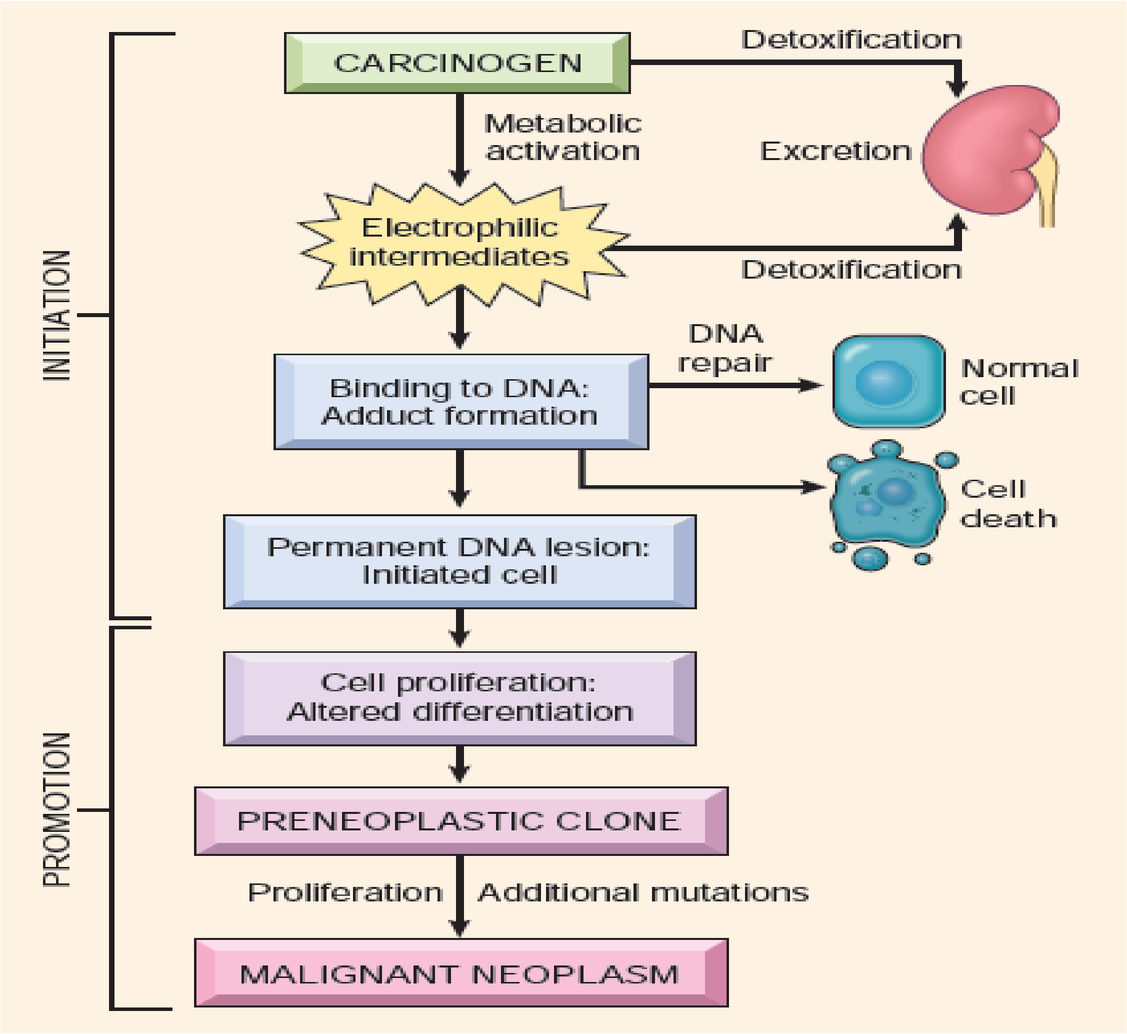
*Initiator*

INITIATED (MUTATED) CELLS

*Promoter*

*Persistent
exposure to initiator*

CANCER CELLS



INITIATION

PROMOTION

CARCINOGEN

Metabolic activation

Detoxification

Excretion

Electrophilic intermediates

Detoxification

Binding to DNA: Adduct formation

DNA repair

Normal cell

Cell death

Permanent DNA lesion: Initiated cell

Cell proliferation: Altered differentiation

PRENEOPLASTIC CLONE

Proliferation

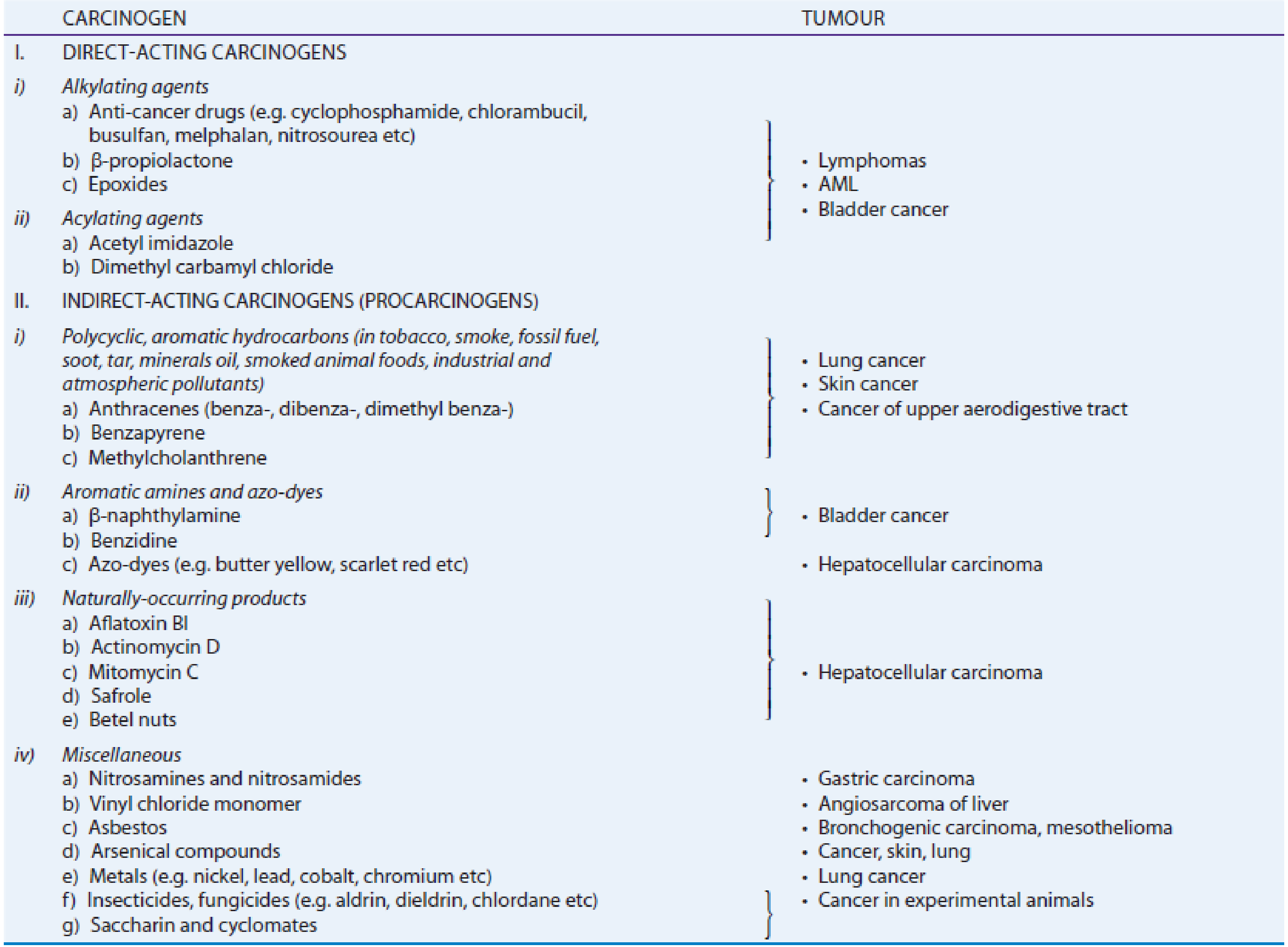
Additional mutations

MALIGNANT NEOPLASM

# Types of chemical carcinogens

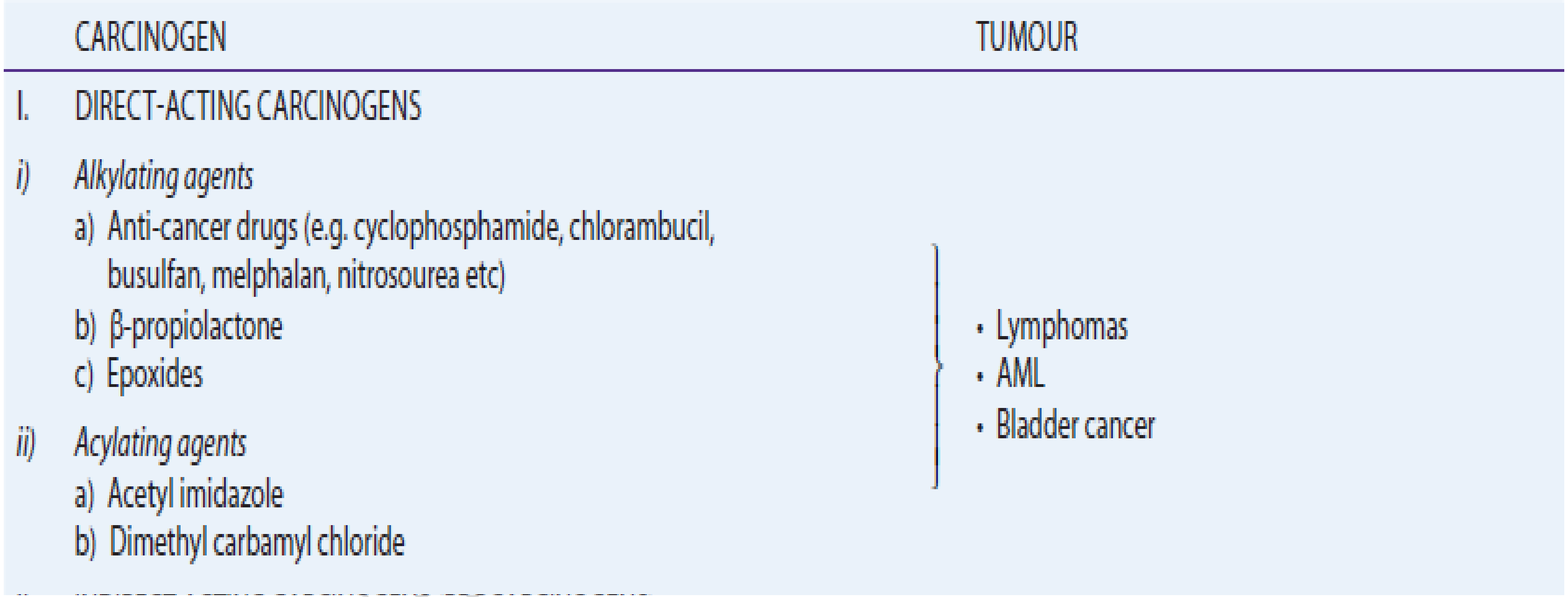
- **Direct-acting carcinogens** → induce cellular transformation without undergoing any prior metabolic activation

- **Indirect-acting carcinogens or procarcinogens** → require metabolic conversion within the body so as to become ‘ultimate’ carcinogens



|  | CARCINOGEN | TUMOUR |
|---|---|---|
| I. | DIRECT-ACTING CARCINOGENS |  |
| *i)* | *Alkylating agents* |  |
|  | a) Anti-cancer drugs (e.g. cyclophosphamide, chlorambucil, busulfan, melphalan, nitrosourea etc) | • Lymphomas<br>• AML<br>• Bladder cancer |
|  | b) β-propiolactone |  |
|  | c) Epoxides |  |
| *ii)* | *Acylating agents* |  |
|  | a) Acetyl imidazole |  |
|  | b) Dimethyl carbamyl chloride |  |
| II. | INDIRECT-ACTING CARCINOGENS (PROCARCINOGENS) |  |
| *i)* | *Polycyclic, aromatic hydrocarbons (in tobacco, smoke, fossil fuel, soot, tar, minerals oil, smoked animal foods, industrial and atmospheric pollutants)* | • Lung cancer<br>• Skin cancer<br>• Cancer of upper aerodigestive tract |
|  | a) Anthracenes (benza-, dibenza-, dimethyl benza-) |  |
|  | b) Benzapyrene |  |
|  | c) Methylcholanthrene |  |
| *ii)* | *Aromatic amines and azo-dyes* |  |
|  | a) β-naphthylamine | • Bladder cancer |
|  | b) Benzidine |  |
|  | c) Azo-dyes (e.g. butter yellow, scarlet red etc) | • Hepatocellular carcinoma |
| *iii)* | *Naturally-occurring products* |  |
|  | a) Aflatoxin BI | • Hepatocellular carcinoma |
|  | b) Actinomycin D |  |
|  | c) Mitomycin C |  |
|  | d) Safrole |  |
|  | e) Betel nuts |  |
| *iv)* | *Miscellaneous* |  |
|  | a) Nitrosamines and nitrosamides | • Gastric carcinoma |
|  | b) Vinyl chloride monomer | • Angiosarcoma of liver |
|  | c) Asbestos | • Bronchogenic carcinoma, mesothelioma |
|  | d) Arsenical compounds | • Cancer, skin, lung |
|  | e) Metals (e.g. nickel, lead, cobalt, chromium etc) | • Lung cancer |
|  | f) Insecticides, fungicides (e.g. aldrin, dieldrin, chlordane etc) | • Cancer in experimental animals |
|  | g) Saccharin and cyclomates |  |

**Dr. PRIYANKA SACHDEV**



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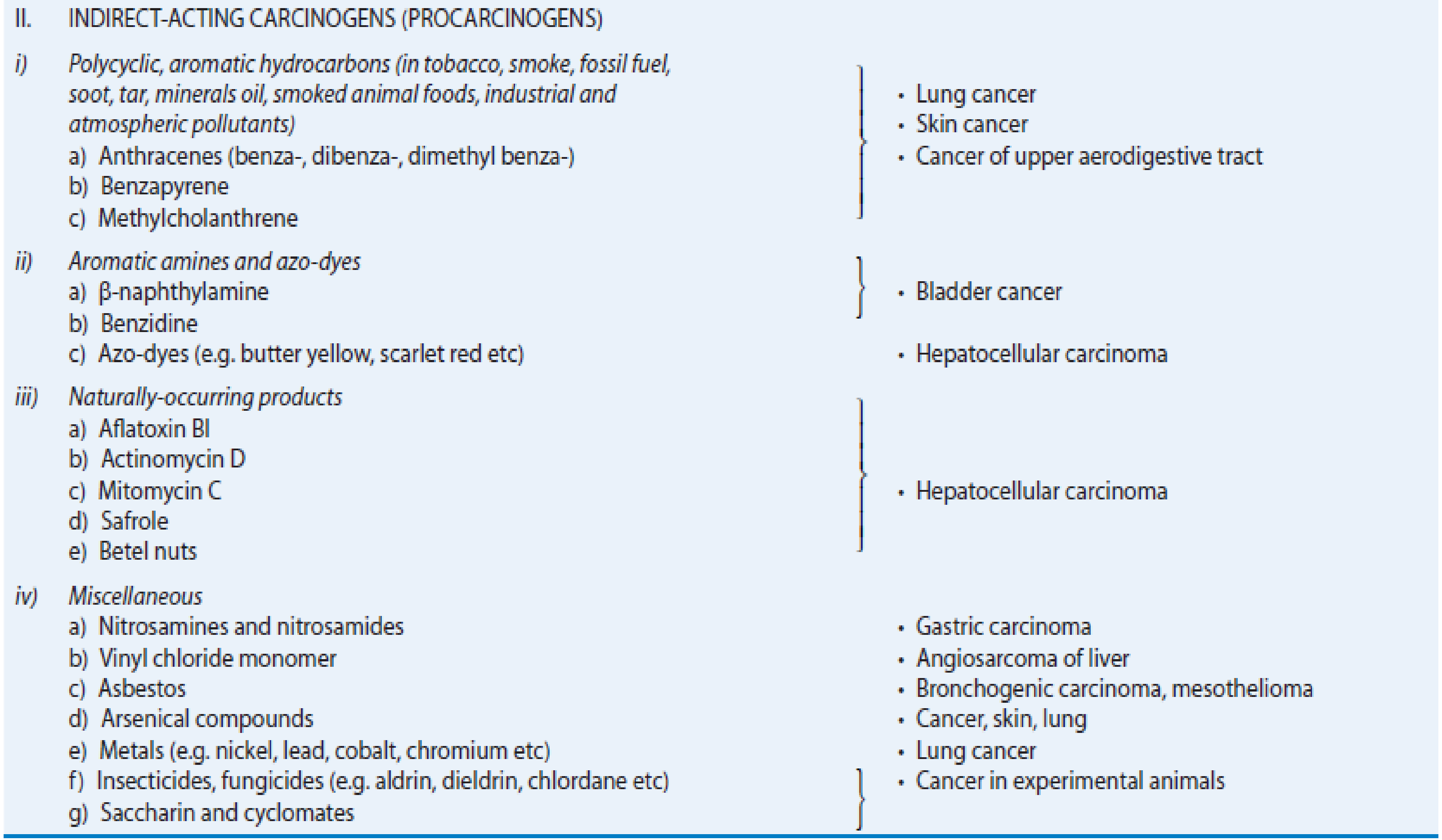
Dr.



| | | |
|---|---|---|
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# STAGES IN CHEMICAL CARCINOGENESIS

3 stages→

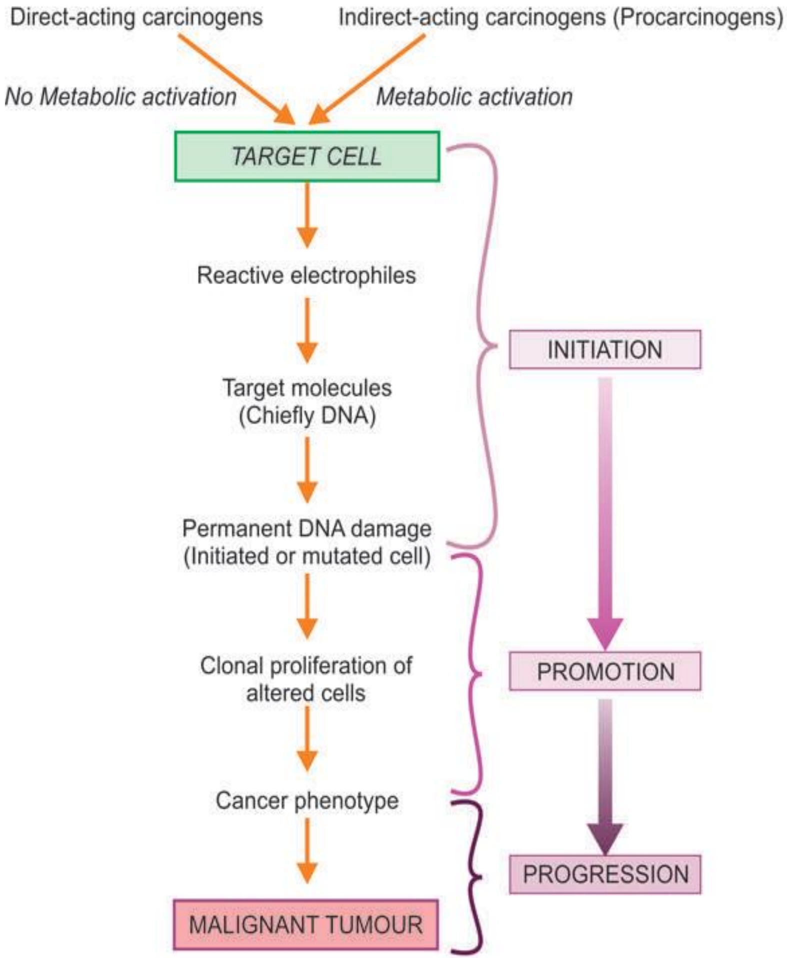
- Initiation
- Promotion
- Progression

# Initiation of Carcinogenesis

1. Metabolic activation
2. Reactive electrophiles
3. Target molecules mutations
4. The initiated cell

# 1.Metabolic activation →

- **Indirect-acting or procarcinogens** require to be activated in liver by the mono-oxygenases of the cytochrome, P-450 system in ER



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(Chiefly DNA)

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Clonal proliferation of
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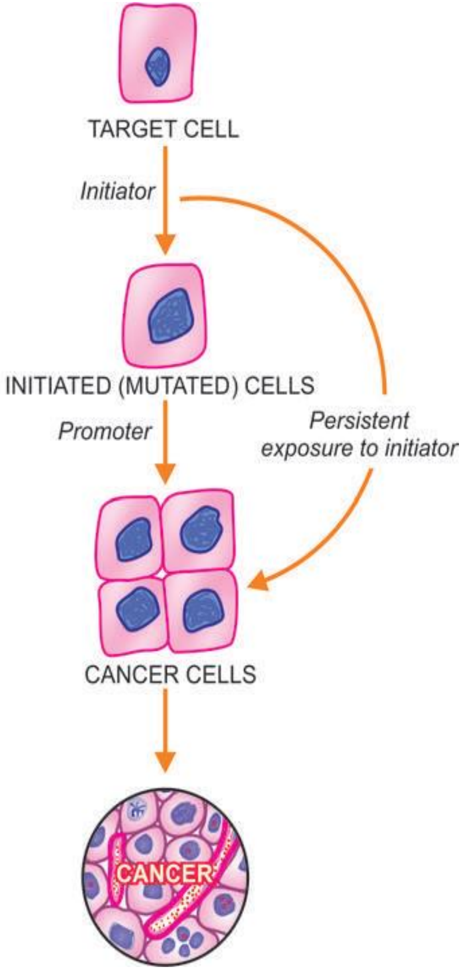
Cancer phenotype

MALIGNANT TUMOUR

INITIATION

PROMOTION

PROGRESSION



TARGET CELL

*Initiator*

INITIATED (MUTATED) CELLS

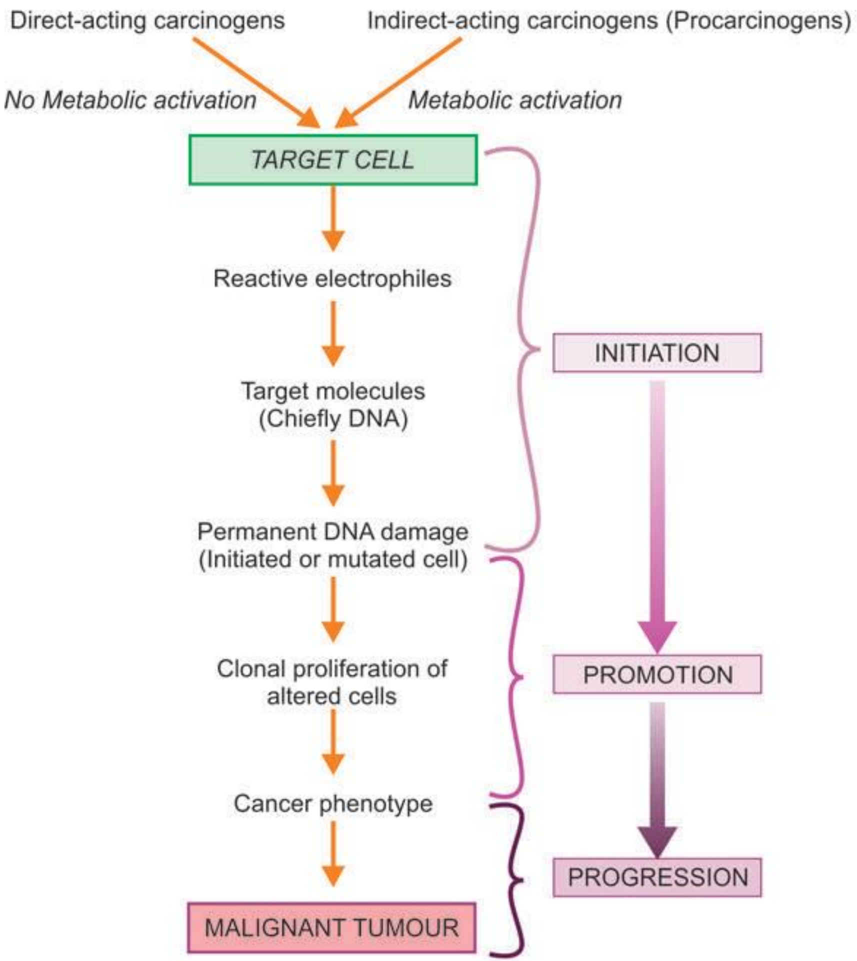
*Promoter*

*Persistent*
*exposure to initiator*

CANCER CELLS

# 2. Reactive electrophiles

- Direct-acting carcinogens are intrinsically **electrophilic (electron deficient)**
- Indirect-acting substances become electron-deficient after metabolic activation i.e. they become reactive electrophiles.
- Following this step, both types of chemical carcinogens behave alike
- Reactive electrophiles bind to electron-rich portions of DNA



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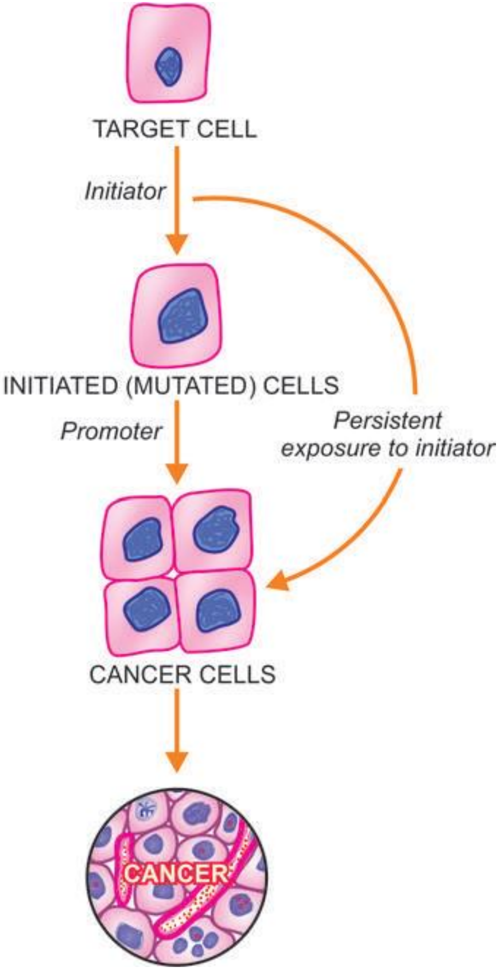
PROMOTION

PROGRESSION



TARGET CELL

*Initiator*

INITIATED (MUTATED) CELLS

*Promoter*

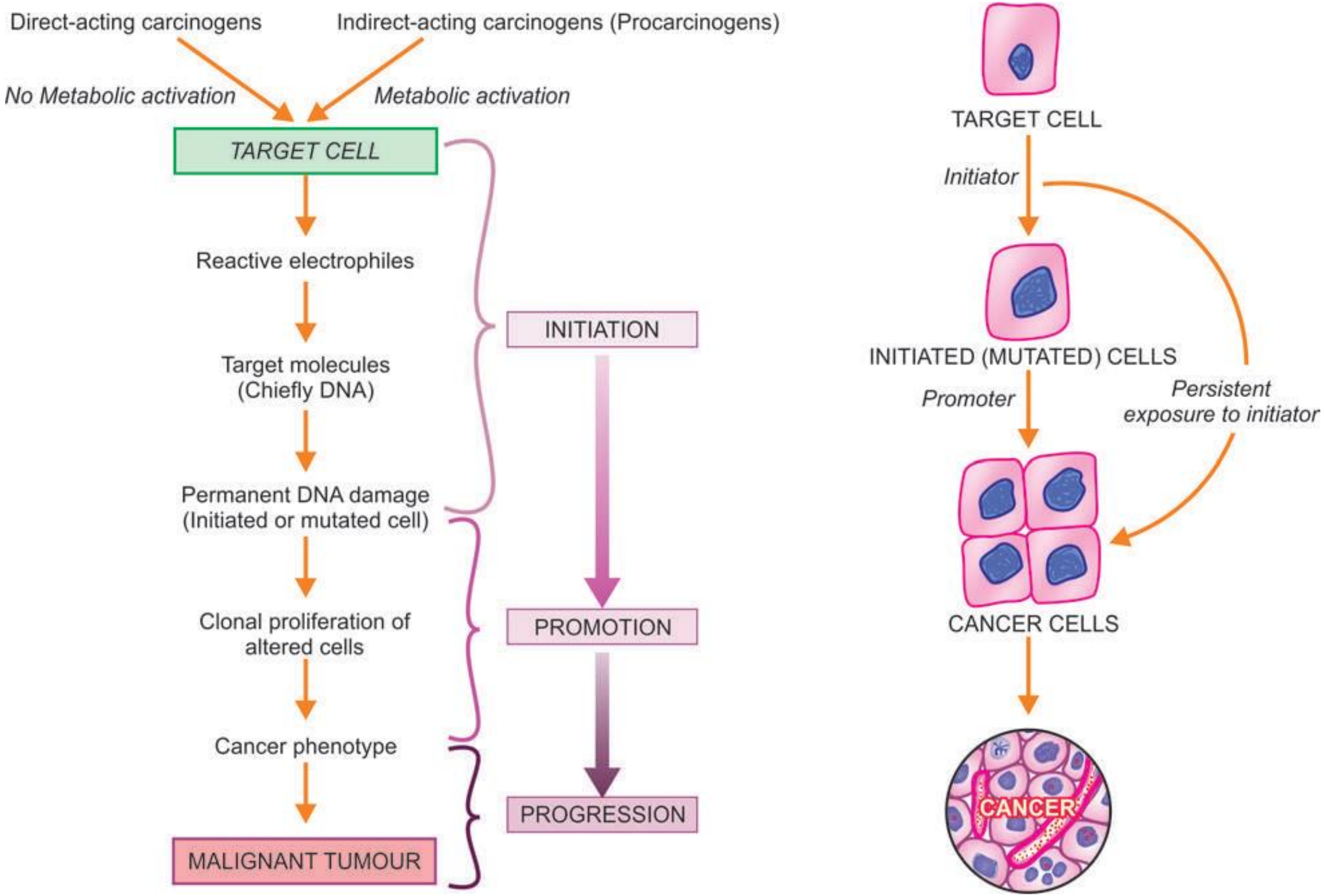
*Persistent exposure to initiator*

CANCER CELLS

# 3. Target molecules mutations

- Primary target of electrophiles is **DNA**
- Produces **mutagenesis**

- ➢Any gene may be the target molecule
- ➢Most frequently affected proto oncogene is **RAS** gene mutation
- ➢Tumour suppressor gene is **p53** gene mutation.



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INITIATION

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INITIATED (MUTATED) CELLS

*Promoter*

*Persistent
exposure to initiator*

CANCER CELLS

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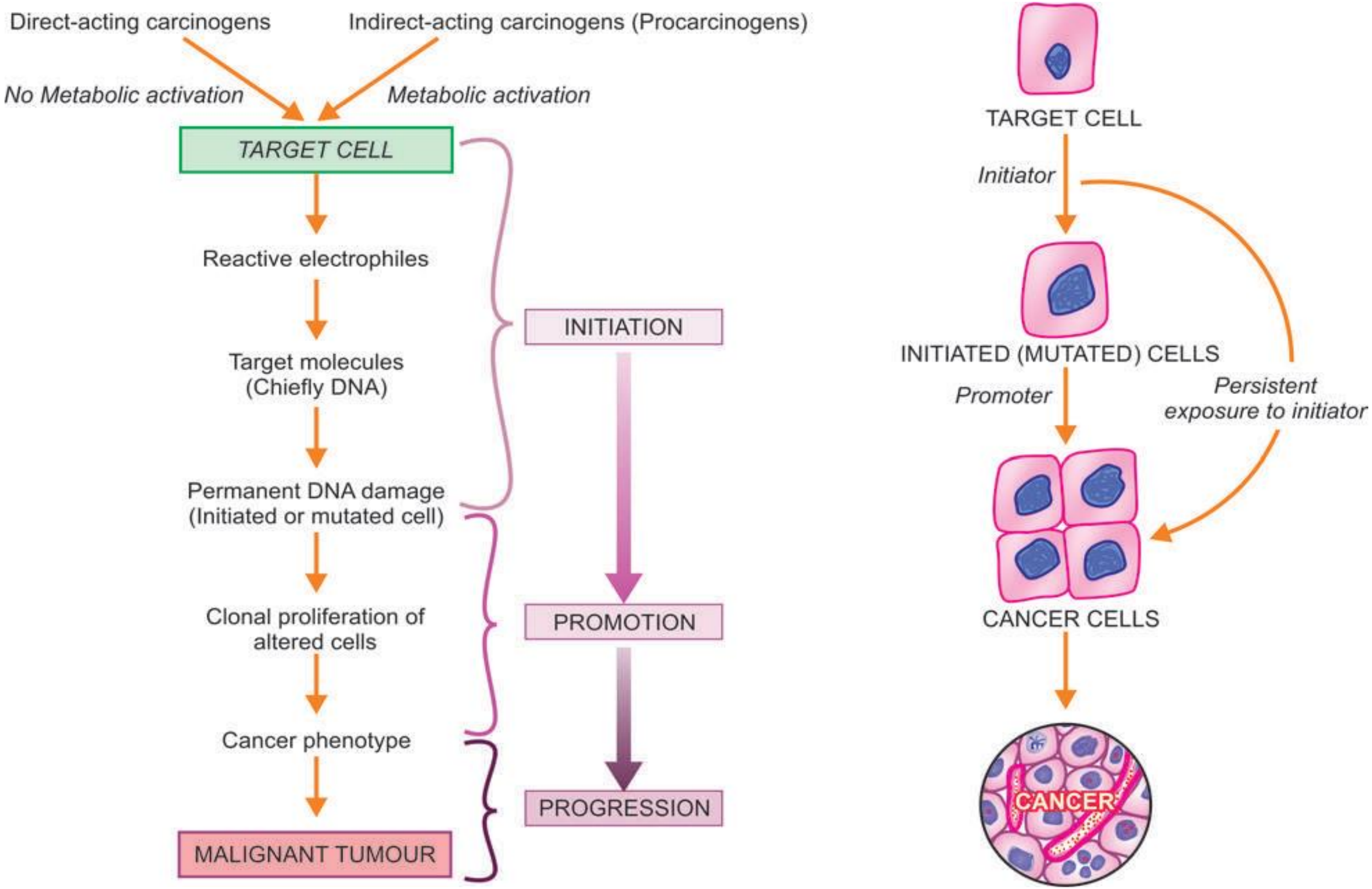
# 4. The initiated cell

The unrepaired damage produced in the DNA of the cell becomes permanent and fixed only if the **altered cell undergoes at least one cycle of proliferation.**

- Results in transferring the change to the next progeny of cells
- so that the **DNA damage becomes permanent and irreversible**



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CANCER CELLS

**Dr. PRIYANKA SACHDEV**

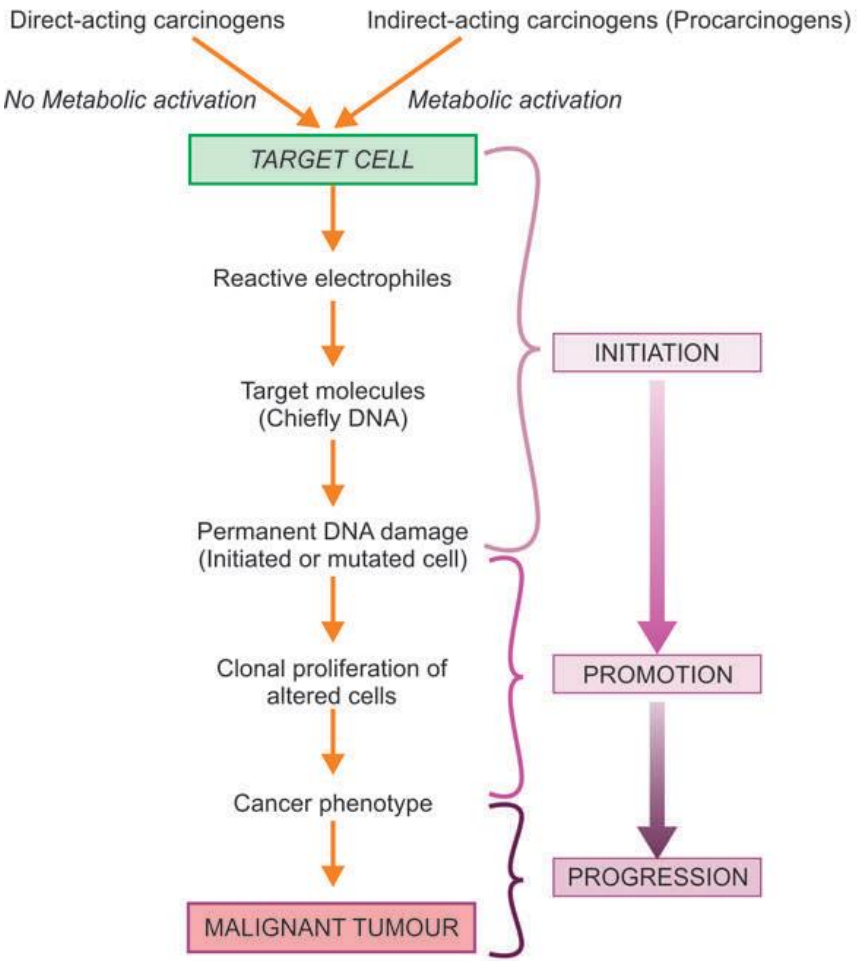
# STAGES IN CHEMICAL CARCINOGENESIS

3 stages→

- Initiation
- Promotion
- Progression

# Promotion of Carcinogenesis

- Promoter carcinogens **do not damage the DNA per se** and are thus not mutagenic
- But instead **enhance the effect of initiators**
- They cause **clonal proliferation and expansion of initiated (mutated) cells**
- They do not produce sudden change.
- The change induced may be **reversible.**



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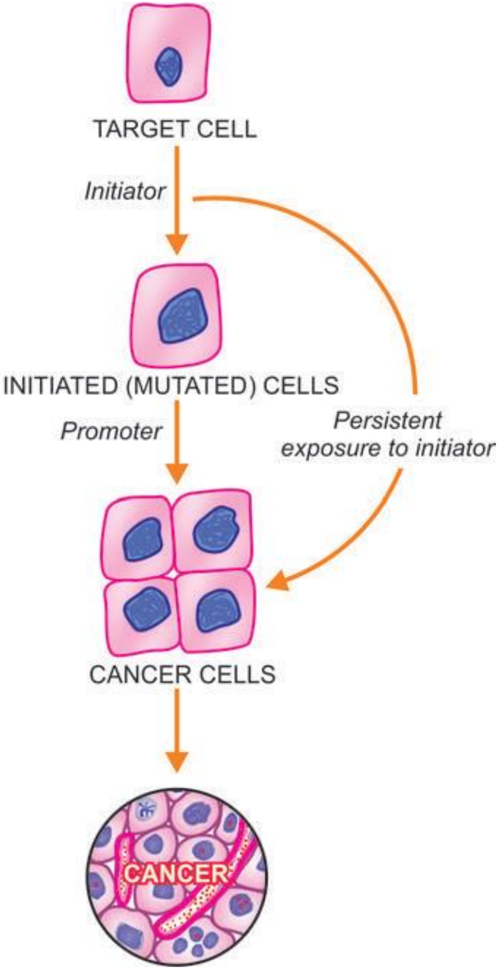


TARGET CELL

*Initiator*

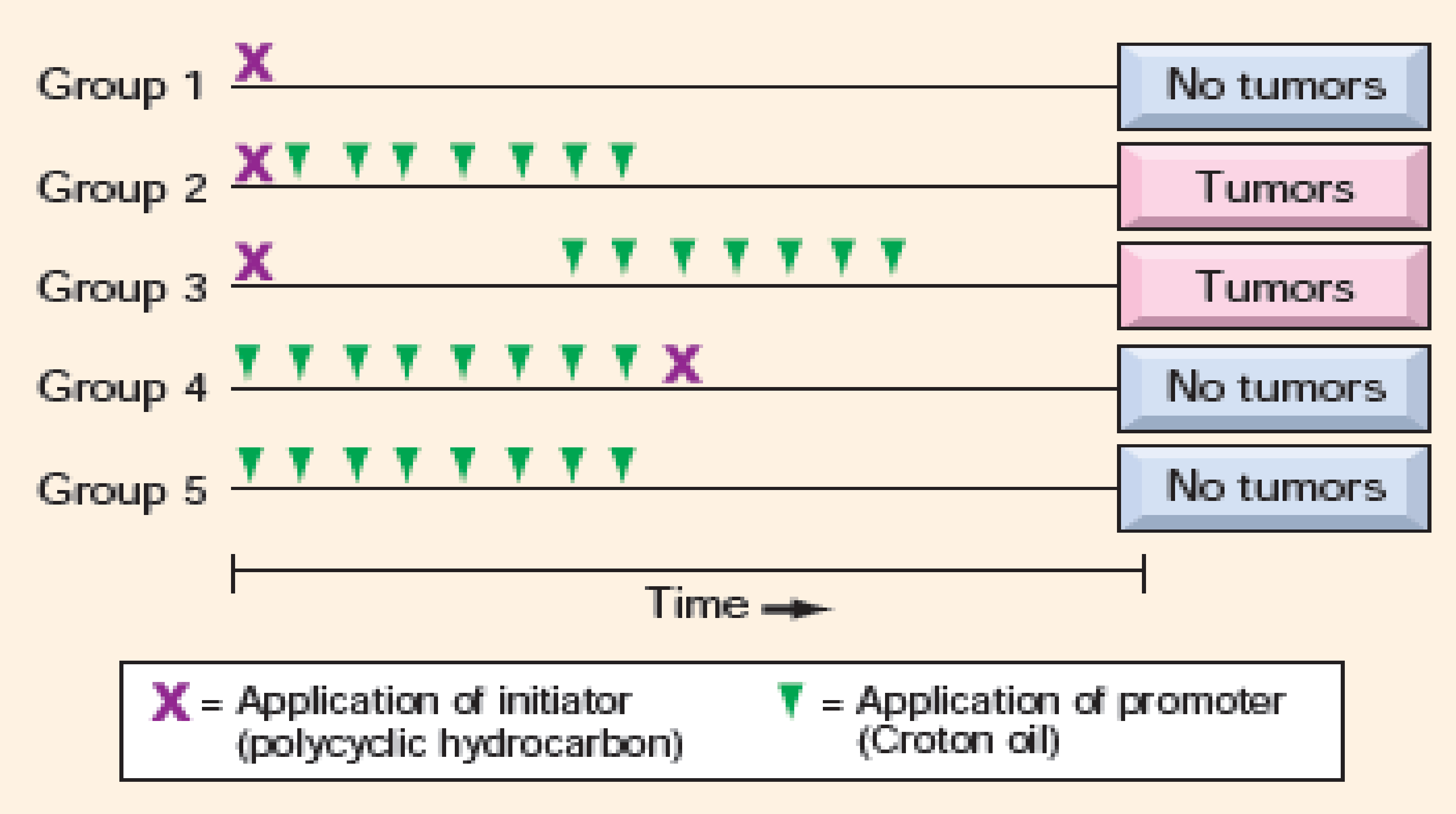
INITIATED (MUTATED) CELLS

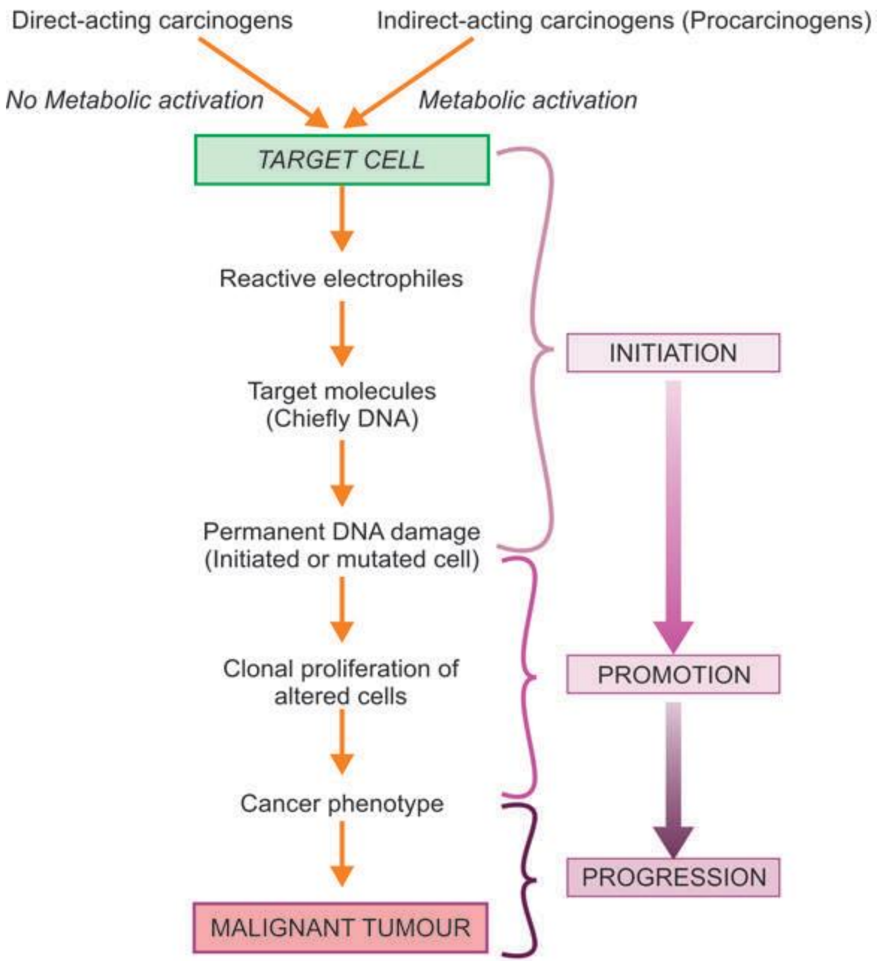
*Promoter*

*Persistent exposure to initiator*

CANCER CELLS

- To produce tumour → **initiator should be followed by promoter**


Group 1
No tumors
Group 2
Tumors
Group 3
Tumors
Group 4
No tumors
Group 5
No tumors
Time
X = Application of initiator (polycyclic hydrocarbon)
= Application of promoter (Croton oil)



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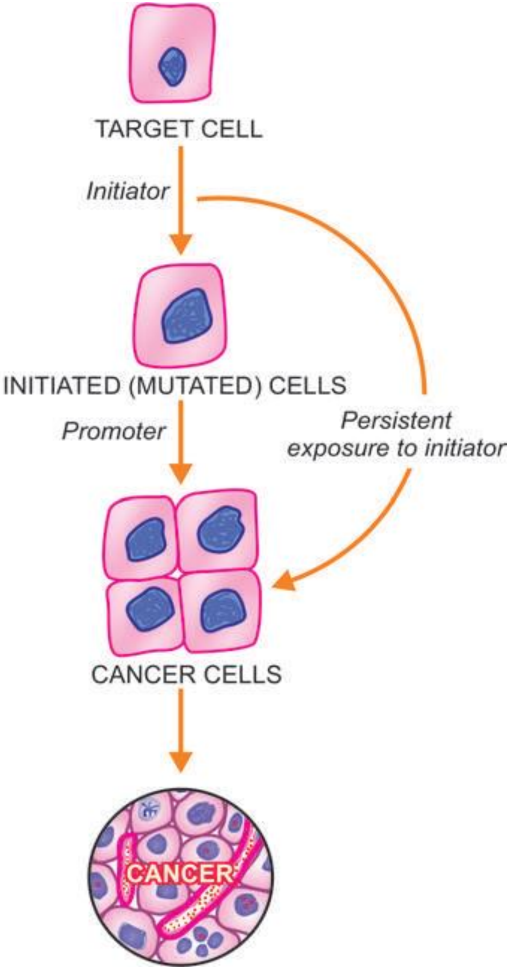
MALIGNANT TUMOUR

INITIATION

PROMOTION

PROGRESSION



TARGET CELL

*Initiator*

INITIATED (MUTATED) CELLS

*Promoter*

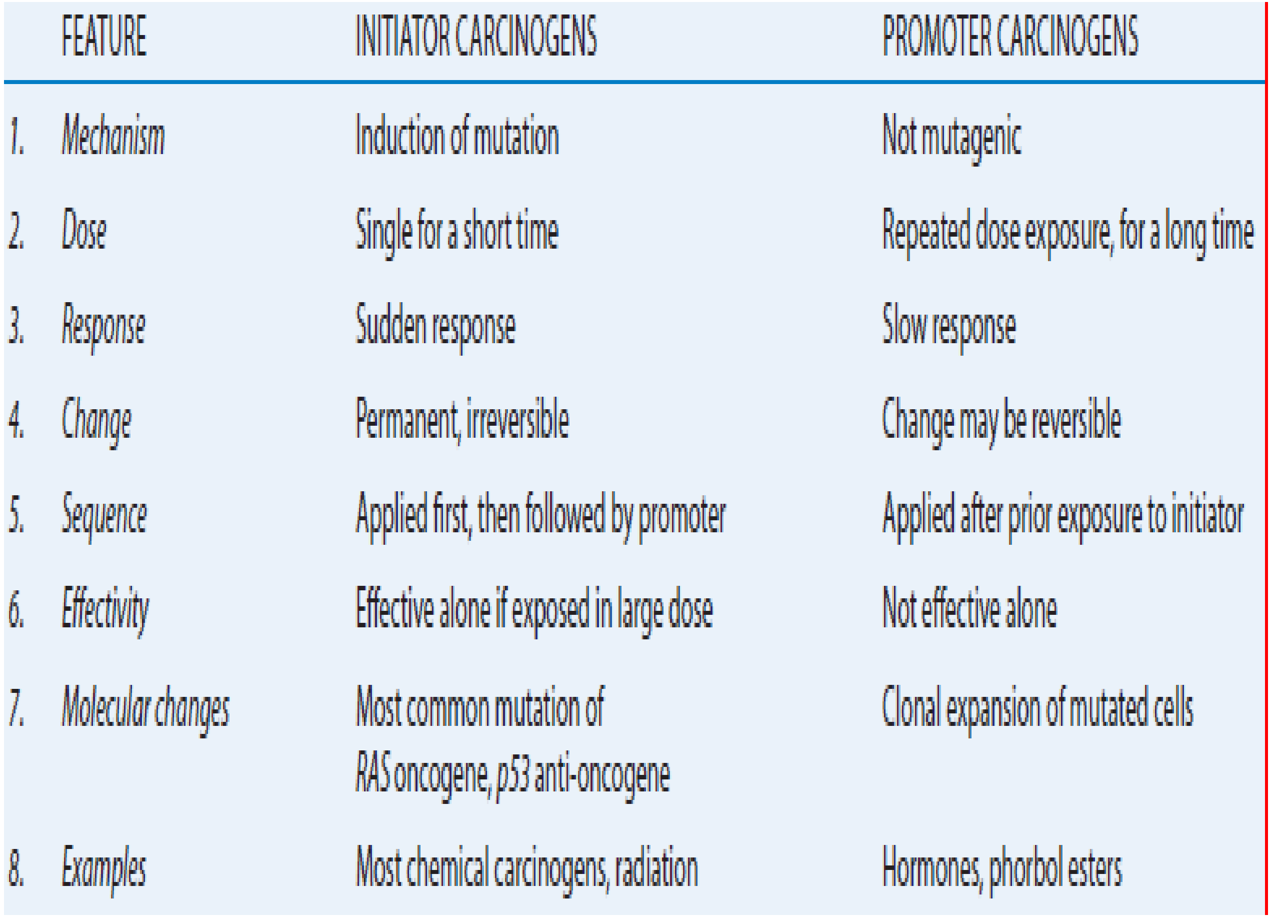
*Persistent*
*exposure to initiator*

CANCER CELLS

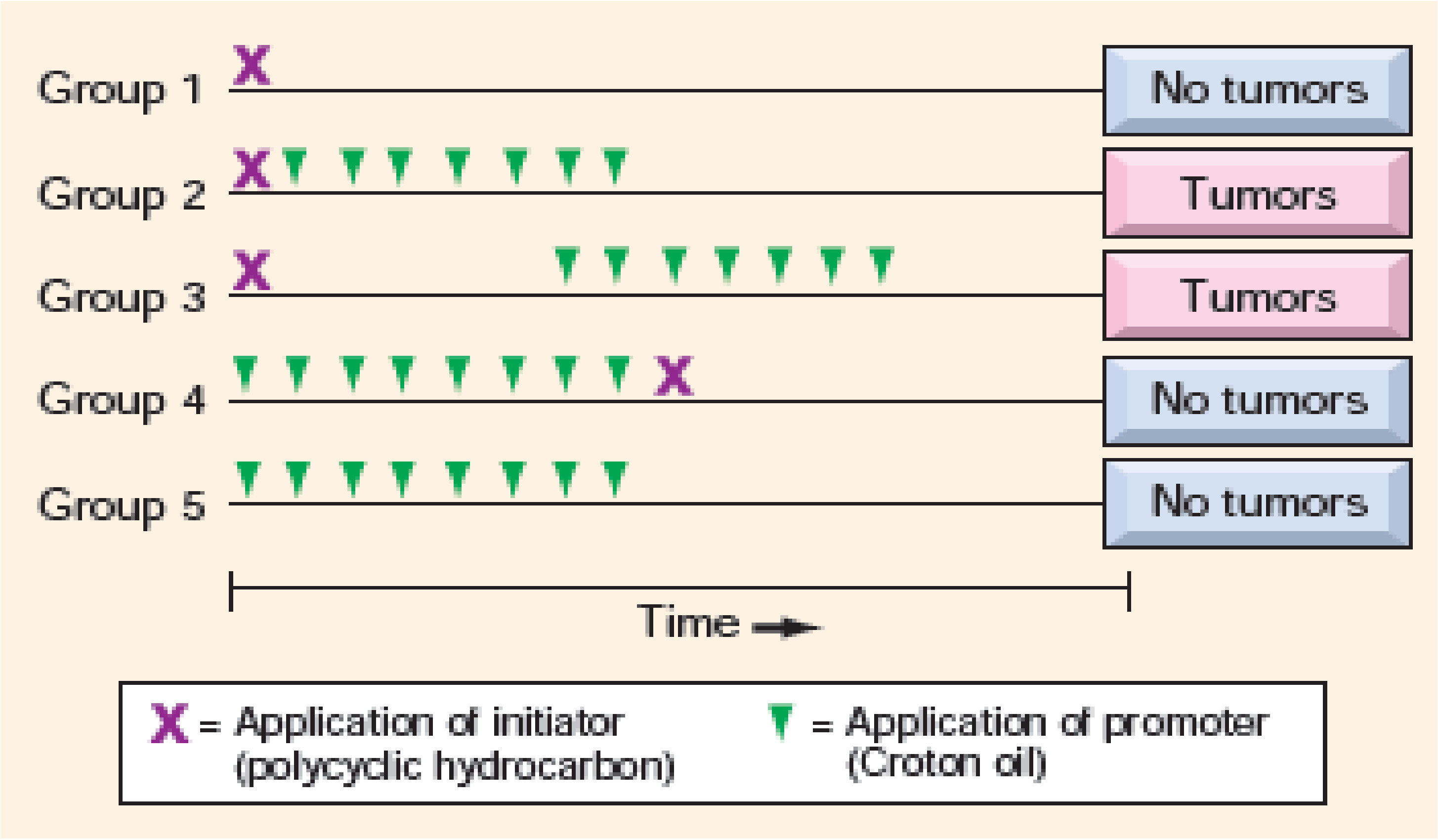
- **Initiators** cause **irreversible DNA damage.**

- **Promoters** cause **reversible DNA damage.**

- The chemical which acts as both initiator as well as promotor is called **complete carcinogen.**



| | FEATURE | INITIATOR CARCINOGENS | PROMOTER CARCINOGENS |
|---|---|---|---|
| 1. | *Mechanism* | Induction of mutation | Not mutagenic |
| 2. | *Dose* | Single for a short time | Repeated dose exposure, for a long time |
| 3. | *Response* | Sudden response | Slow response |
| 4. | *Change* | Permanent, irreversible | Change may be reversible |
| 5. | *Sequence* | Applied first, then followed by promoter | Applied after prior exposure to initiator |
| 6. | *Effectivity* | Effective alone if exposed in large dose | Not effective alone |
| 7. | *Molecular changes* | Most common mutation of *RAS* oncogene, *p53* anti-oncogene | Clonal expansion of mutated cells |
| 8. | *Examples* | Most chemical carcinogens, radiation | Hormones, phorbol esters |



Group 1 — No tumors

Group 2 — Tumors

Group 3 — Tumors

Group 4 — No tumors

Group 5 — No tumors

Time →

X = Application of initiator (polycyclic hydrocarbon)

▼ = Application of promoter (Croton oil)

# STAGES IN CHEMICAL CARCINOGENESIS

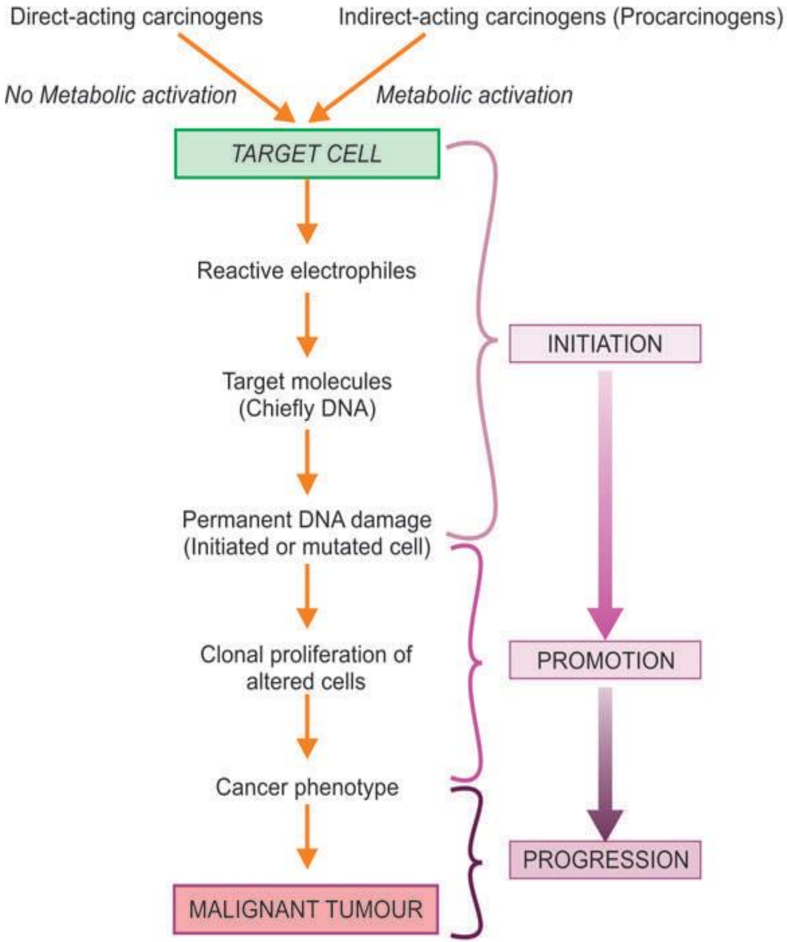
3 stages→

- ➢Initiation
- ➢Promotion
- ➢Progression

# Progression of Carcinogenesis

- Progression of cancer is the stage when mutated proliferated cell shows **phenotypic features of malignancy.**

- Initiated cell proliferate rapidly and in this process acquires more and more mutations



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MALIGNANT TUMOUR

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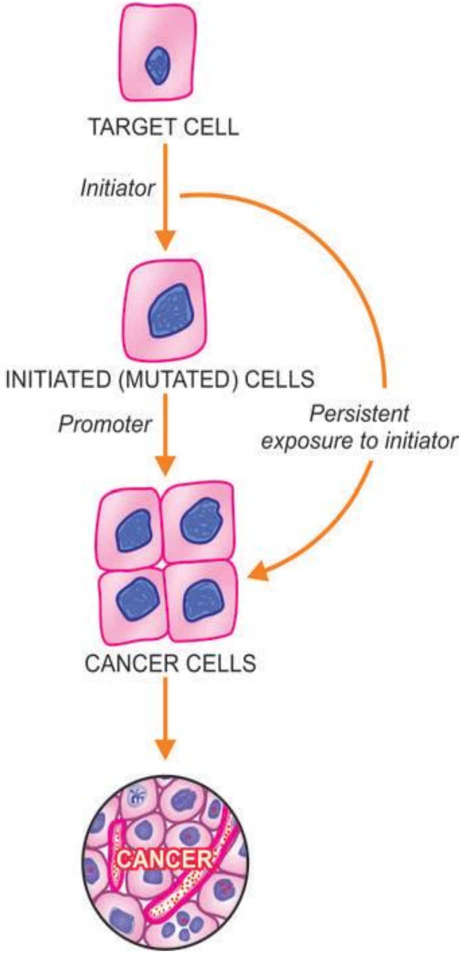

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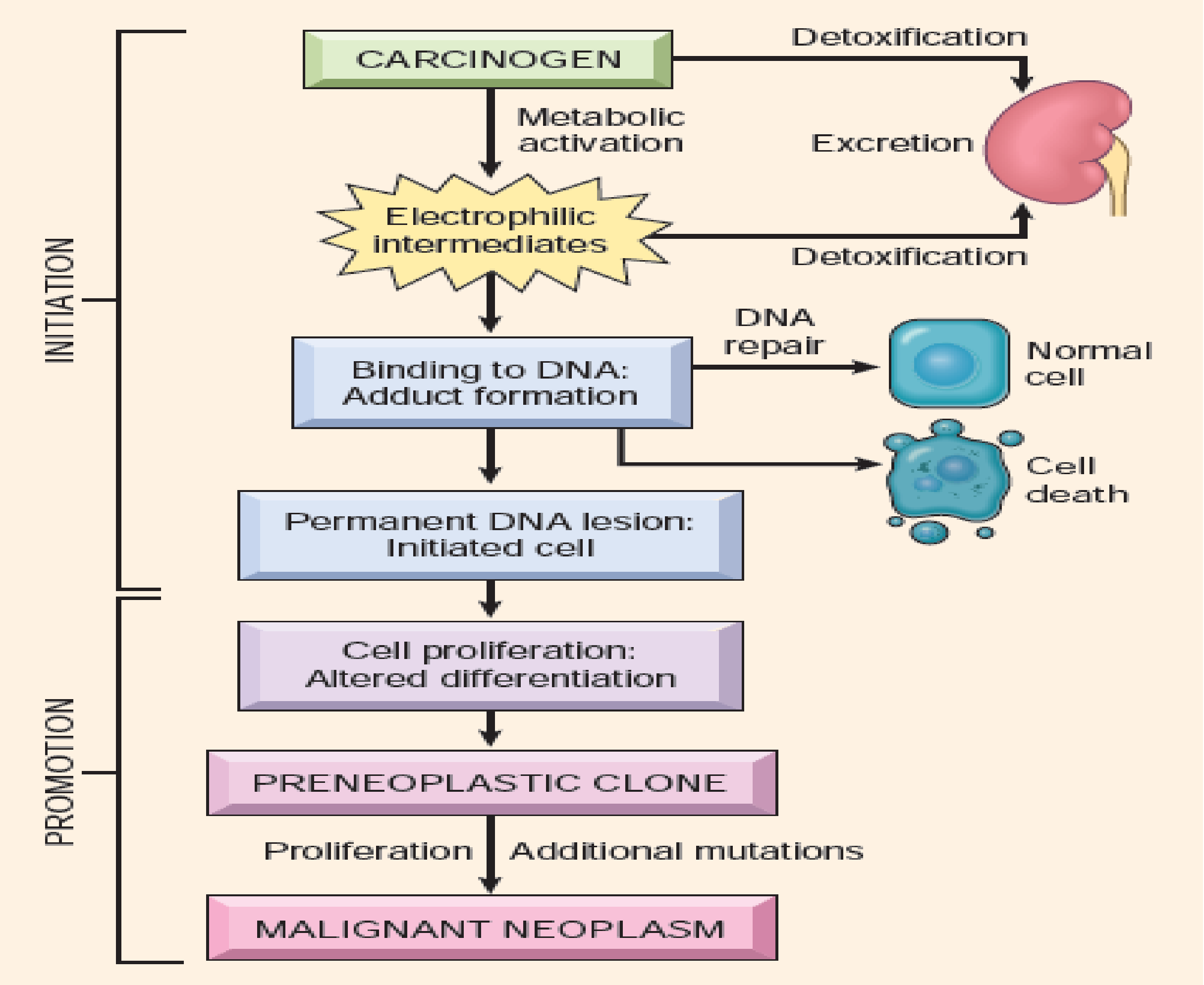
CANCER CELLS

**Dr. PRIYANKA SACHDEV**



INITIATION

PROMOTION

CARCINOGEN

Detoxification

Metabolic activation

Excretion

Electrophilic intermediates

Detoxification

Binding to DNA: Adduct formation

DNA repair

Normal cell

Cell death

Permanent DNA lesion: Initiated cell

Cell proliferation: Altered differentiation

PRENEOPLASTIC CLONE

Proliferation

Additional mutations

MALIGNANT NEOPLASM

**Dr. PRIYANKA SACHDEV**

# TESTS FOR CHEMICAL CARCINOGENICITY

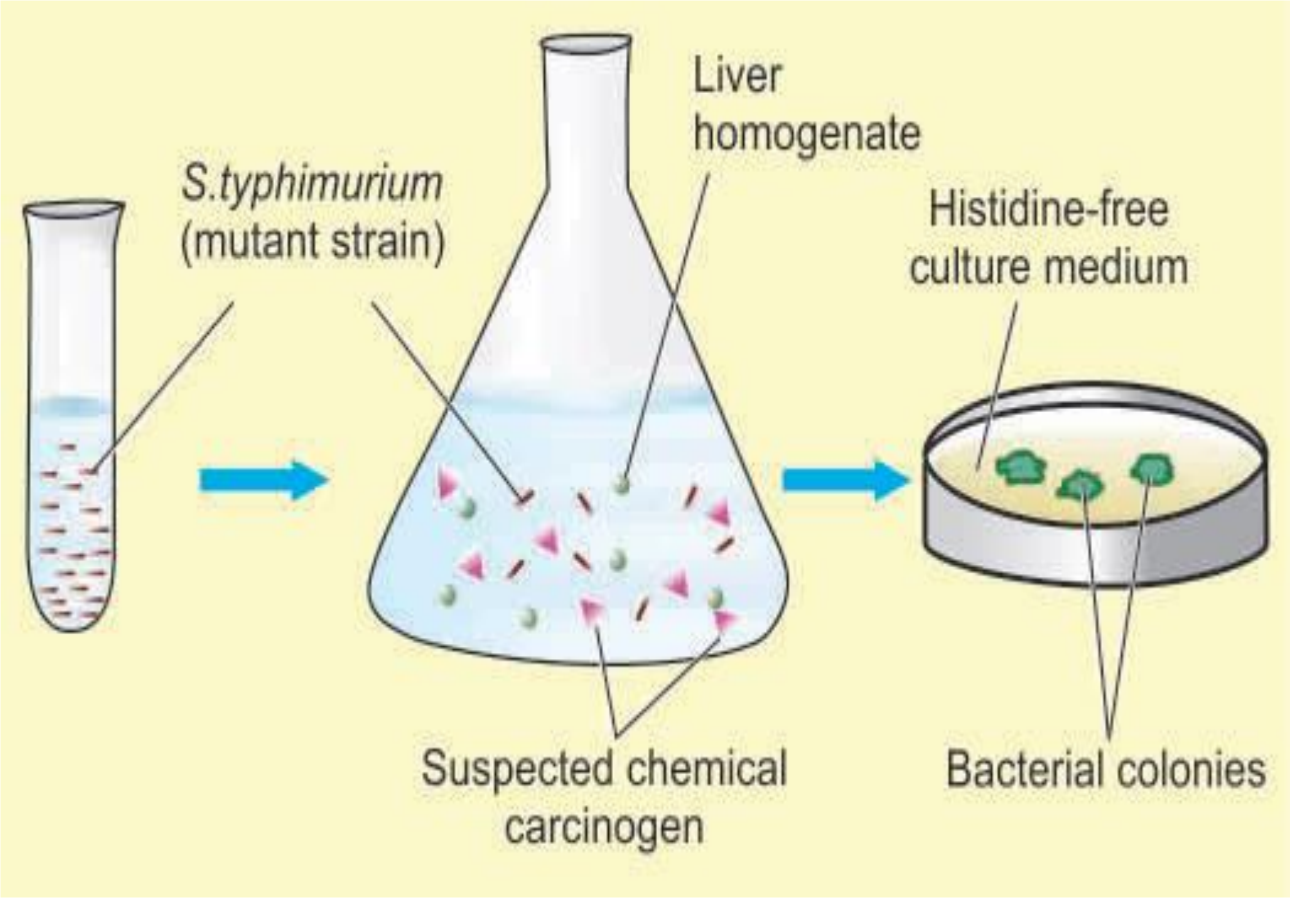
## AMES' TEST

- Evaluates the ability of a chemical to induce mutation in the **mutant strain of Salmonella typhimurium that cannot synthesise histidine.**

- Such strains of **mutant Salmonella typhimurium** are incubated with the potential carcinogen

- If the chemical under test is mutagenic, it will induce mutation in the mutant strains of S. typhimurium in the functional histidine gene

- It will be reflected by the number of bacterial colonies growing on histidine-free culture medium


*S.typhimurium* (mutant strain)
Liver homogenate
Histidine-free culture medium
Suspected chemical carcinogen
Bacterial colonies

**Dr. PRIYANKA SACHDEV**

| **Chemical carcinogens** | **Associated cancer or neoplasm** |
|---|---|
| • ***Alkylating agents*** | Acute myelocytic leukemia, bladder cancer |
| • Androgens | Prostate cancer |
| • ***Aromatic amines (dyes) (aniline dyes)*** | ***Bladder cancer*** *(AIIMS 06)* |
| • Arsenic | Cancer of the lung, skin |
| • ***Asbestos*** | ***Cancer of the lung*** *(AIIMS 06)* ***, pleura, Peritoneum, Mesothelioma*** *(AI 13)* |
| • Estrogens | Cancer of the endometrium liver, breast |
| • Ethyl alcohol | Cancer of the liver, esophagus, head and neck |
| • Tobacco (including smokeless) | Cancer of the upper aerodigestive tract, bladder |
| • Vinyl chloride | Liver cancer (angiosarcoma) |
| • Chromium and nickel | Lung cancer |
| • **Benzene** *(AI 15)* | **Leukemia** *(AI 15)*, Hodgkin's lymphoma |
| • **Nitrates** *(AI 15)* | **Gastric cancer** *(AI 15)* |
| • Aflatoxin | Liver cancer |

- **Sir Percival Pott** demonstrated the increased incidence of **scrotal skin cancer in chimney workers exposed to chemical soot.**

# 3 TYPES→

A. Chemical carcinogens
B. Physical carcinogens
C. Biologic carcinogens

# B. PHYSICAL CARCINOGENESIS

medLIVE

# B. PHYSICAL CARCINOGENESIS

1. **Radiation**→ ultraviolet light and ionising radiation

2. **Non-radiation physical agents**→ injuries

# RADIATION CARCINOGENESIS

- ULTRAVIOLET LIGHT
- IONISING RADIATION

# ULTRAVIOLET LIGHT

- source → sunlight
- skin cancers—squamous Cell carcinoma, basal cell carcinoma and melanoma.

- Basal cell carcinoma is the most common cancer due to excessive UV light exposure.

- has three subtypes

1. **UV-A** is 320-400 nm
2. **UV-B** is 280- 320 nm
3. **UV-C** is 200 - 280 nm

- **UV-C** gets filtered by ozone layer
- **UV-B** is the most carcinogenic UV ray to reach the earth

(**UV-B** is Bad for humans as it causes cancers)

# Mechanism

Exposure to UV rays

↓

Pyrimidine dimers in DNA

↓

Mutation in oncogenes and tumor suppressor genes

↓

Cancer

# RADIATION CARCINOGENESIS

- ULTRAVIOLET LIGHT

- IONISING RADIATION

# IONISING RADIATION

- **Source→ x-rays, y rays , α rays, β particles**

- **Cancers→**

1. **All forms of leukaemias (except chronic lymphocytic leukaemia CLL),**
2. **Cancers of the thyroid (most commonly papillary carcinoma)**
3. skin, breast, ovary, uterus, lung, myeloma, and salivary glands

- Maximum sensitivity is at **G2 stage**

# Mechanism

Exposure to ionizing radiation

↓

dislodge ions from water

↓

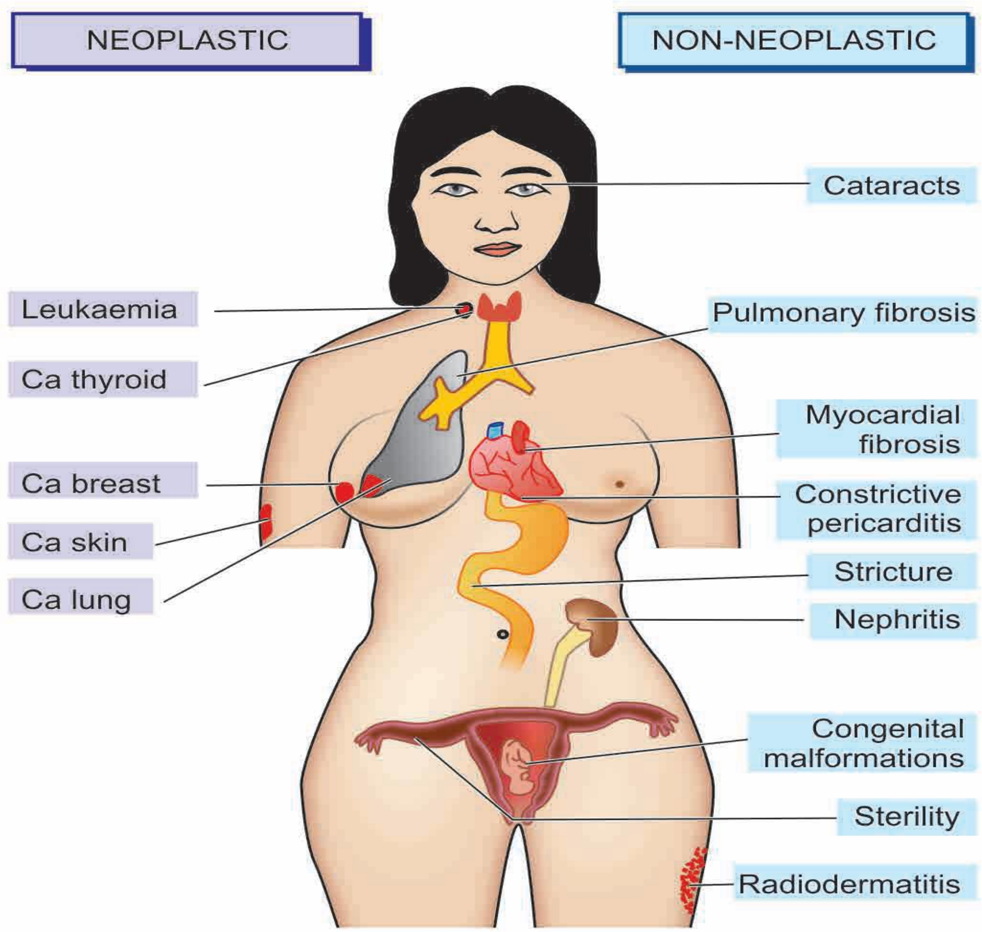
formation of highly reactive free radicals

↓

DNA damage

↓

Cancer


NEOPLASTIC
NON-NEOPLASTIC
Cataracts
Leukaemia
Pulmonary fibrosis
Ca thyroid
Myocardial fibrosis
Ca breast
Constrictive pericarditis
Ca skin
Stricture
Ca lung
Nephritis
Congenital malformations
Sterility
Radiodermatitis

Dr

**Dr. PRIYANKA SACHDEV**

# NON-RADIATION PHYSICAL CARCINOGENESIS

Mechanical injury to the tissues →

- i) Stones in the gallbladder→ cancer
- ii) Healed scars following burns → cancer

# REMEMBER

- **CLL** is the only leukemia NOT associated with ionizing radiation exposure.

# REMEMBER

- The **most radiosensitive** cell in the **blood** is the **lymphocytes**
- The **least radiosensitive** cell in the **blood** is the **platelets**
- **DNA** is the most sensitive intracellular organelle to radiation.

# 3 TYPES→

A. Chemical carcinogens
B. Physical carcinogens
C. Biologic carcinogens

# C. BIOLOGIC CARCINOGENESIS

# VIRAL CARCINOGENESIS

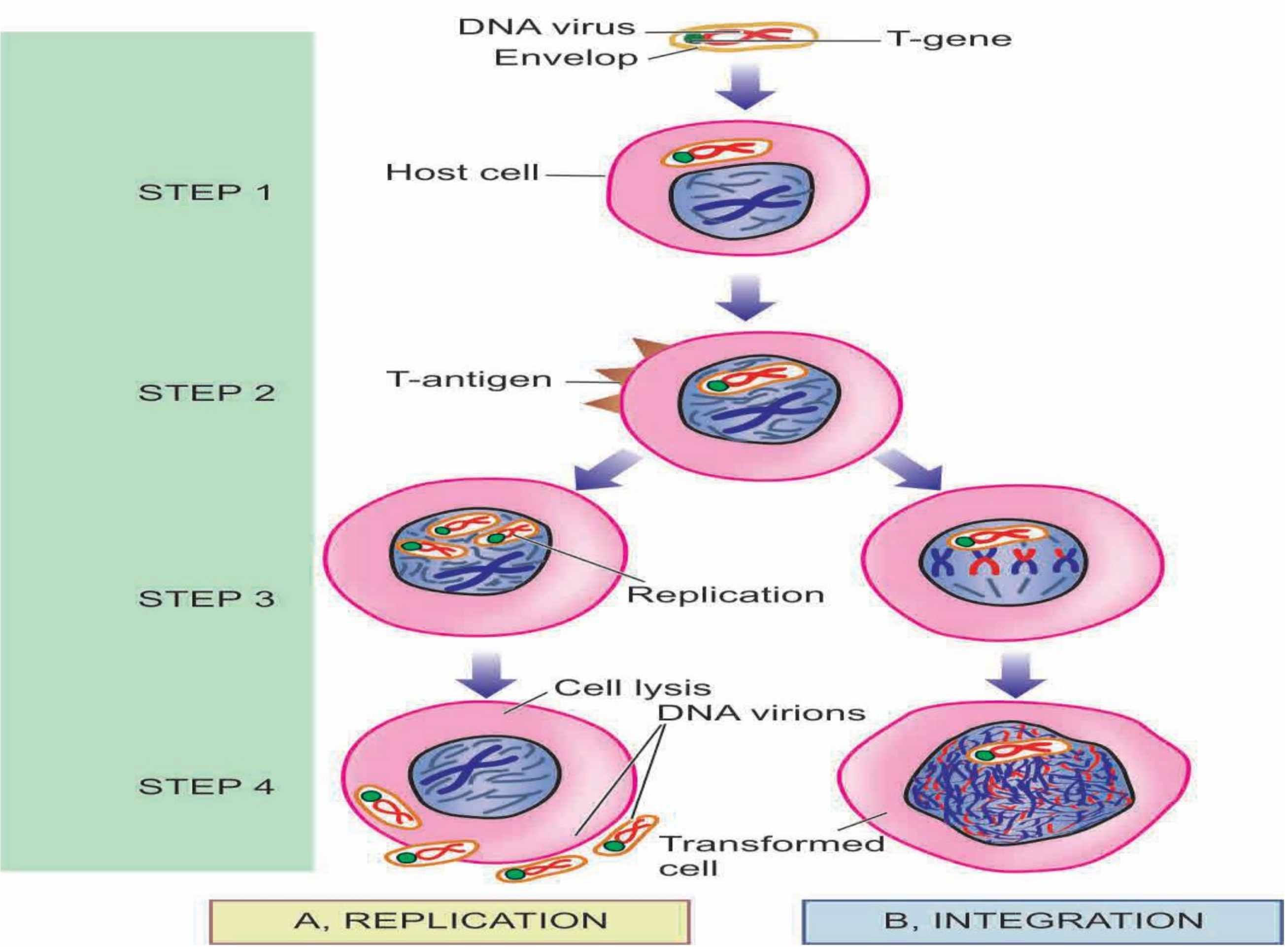
- Based on their nucleic acid content, oncogenic viruses 2 types→

1. DNA oncogenic viruses
2. RNA oncogenic viruses or retroviruses

# 1. Mode of DNA viral oncogenesis

- **Replication** The virus may replicate in the host cell with consequent lysis of the infected cell and release of virions→ **cell death**

- **Integration** The viral DNA may integrate into the host cell DNA → induction of mutation→**neoplastic transformation of the host cell**


DNA virus
Envelop
T-gene
STEP 1
Host cell
STEP 2
T-antigen
STEP 3
Replication
STEP 4
Cell lysis
DNA virions
Transformed cell
A, REPLICATION
B, INTEGRATION

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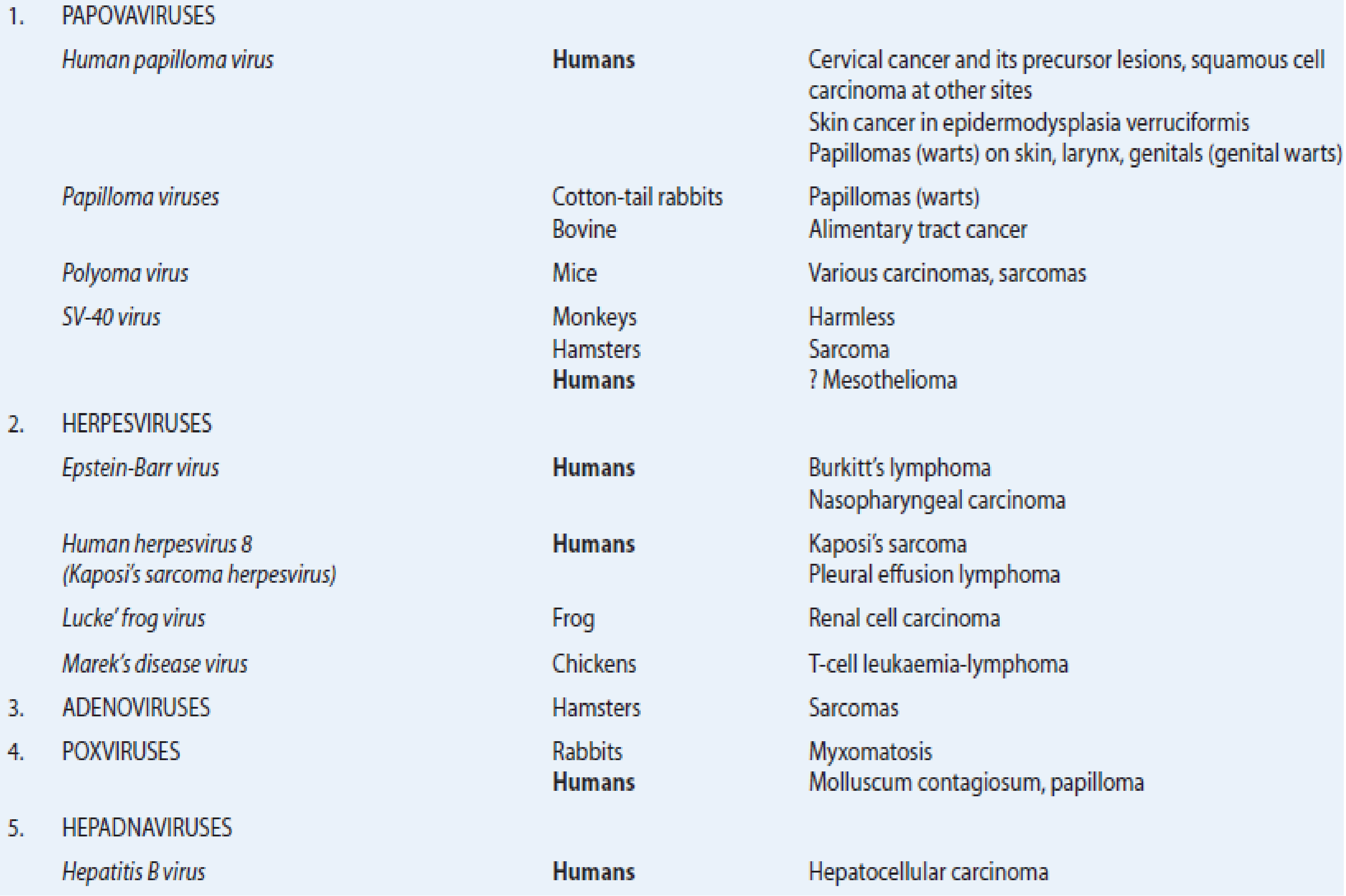


| | | | |
|---|---|---|---|
| 1. | PAPOVAVIRUSES | | |
| | *Human papilloma virus* | **Humans** | Cervical cancer and its precursor lesions, squamous cell carcinoma at other sites<br>Skin cancer in epidermodysplasia verruciformis<br>Papillomas (warts) on skin, larynx, genitals (genital warts) |
| | *Papilloma viruses* | Cotton-tail rabbits | Papillomas (warts) |
| | | Bovine | Alimentary tract cancer |
| | *Polyoma virus* | Mice | Various carcinomas, sarcomas |
| | *SV-40 virus* | Monkeys | Harmless |
| | | Hamsters | Sarcoma |
| | | **Humans** | ? Mesothelioma |
| 2. | HERPESVIRUSES | | |
| | *Epstein-Barr virus* | **Humans** | Burkitt's lymphoma<br>Nasopharyngeal carcinoma |
| | *Human herpesvirus 8 (Kaposi's sarcoma herpesvirus)* | **Humans** | Kaposi's sarcoma<br>Pleural effusion lymphoma |
| | *Lucke' frog virus* | Frog | Renal cell carcinoma |
| | *Marek's disease virus* | Chickens | T-cell leukaemia-lymphoma |
| 3. | ADENOVIRUSES | Hamsters | Sarcomas |
| 4. | POXVIRUSES | Rabbits | Myxomatosis |
| | | **Humans** | Molluscum contagiosum, papilloma |
| 5. | HEPADNAVIRUSES | | |
| | *Hepatitis B virus* | **Humans** | Hepatocellular carcinoma |

# Carcinogenic Viruses

## RNA viruses

- Human T cell leukemia virus-1 (HTLV-1)
- Hepatitis C virus (HCV)

## DNA viruses

- Hepatitis B virus (HBV)
- Human herpes virus 8 (HHV8)
- Human papilloma virus (HPV)
- Epstein-Barr virus (EBV)

# Mode of RNA viral oncogenesis

- RNA oncogenic viruses are retroviruses i.e. they contain the enzyme **reverse transcriptase (RT)**

The viral envelope fuses with the plasma membrane of the host cell

↓

Reverse transcriptase acts as template to synthesise ss of matching viral DNA

↓

It is then copied to form complementary DNA resulting in ds viral DNA **(provirus)**

↓

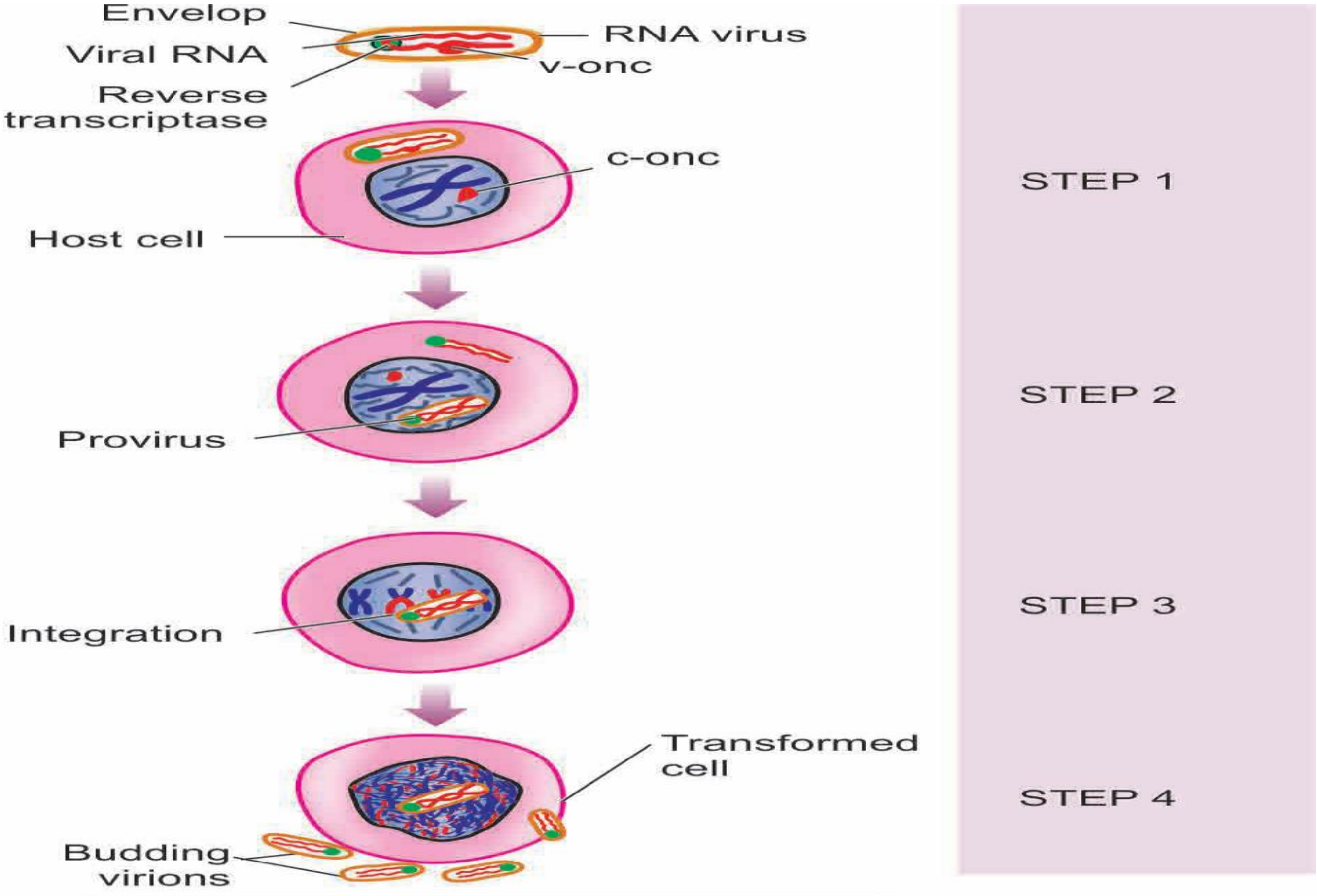
The provirus is integrated into the host cell genome producing **‘transformed host cell’**

↓

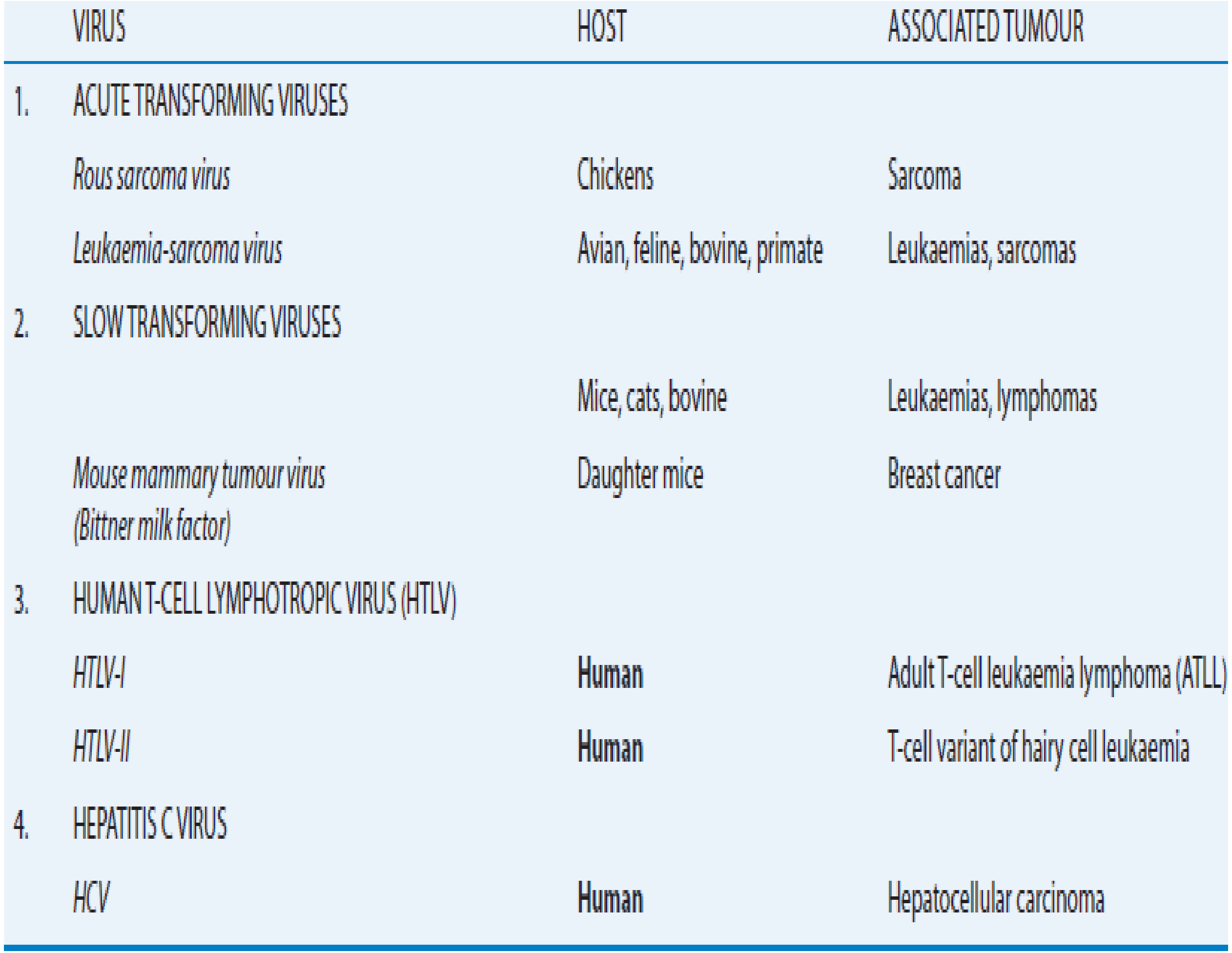
Integration of the provirus brings about replication of viral components

↓

Assembled and released by budding


Envelop
Viral RNA
Reverse transcriptase
RNA virus
v-onc
c-onc
Host cell
STEP 1
Provirus
STEP 2
Integration
STEP 3
Transformed cell
Budding virions
STEP 4

INTEGRATION AND REPLICATION



| | VIRUS | HOST | ASSOCIATED TUMOUR |
|---|---|---|---|
| 1. | ACUTE TRANSFORMING VIRUSES | | |
| | *Rous sarcoma virus* | Chickens | Sarcoma |
| | *Leukaemia-sarcoma virus* | Avian, feline, bovine, primate | Leukaemias, sarcomas |
| 2. | SLOW TRANSFORMING VIRUSES | | |
| | | Mice, cats, bovine | Leukaemias, lymphomas |
| | *Mouse mammary tumour virus (Bittner milk factor)* | Daughter mice | Breast cancer |
| 3. | HUMAN T-CELL LYMPHOTROPIC VIRUS (HTLV) | | |
| | *HTLV-I* | **Human** | Adult T-cell leukaemia lymphoma (ATLL) |
| | *HTLV-II* | **Human** | T-cell variant of hairy cell leukaemia |
| 4. | HEPATITIS C VIRUS | | |
| | *HCV* | **Human** | Hepatocellular carcinoma |

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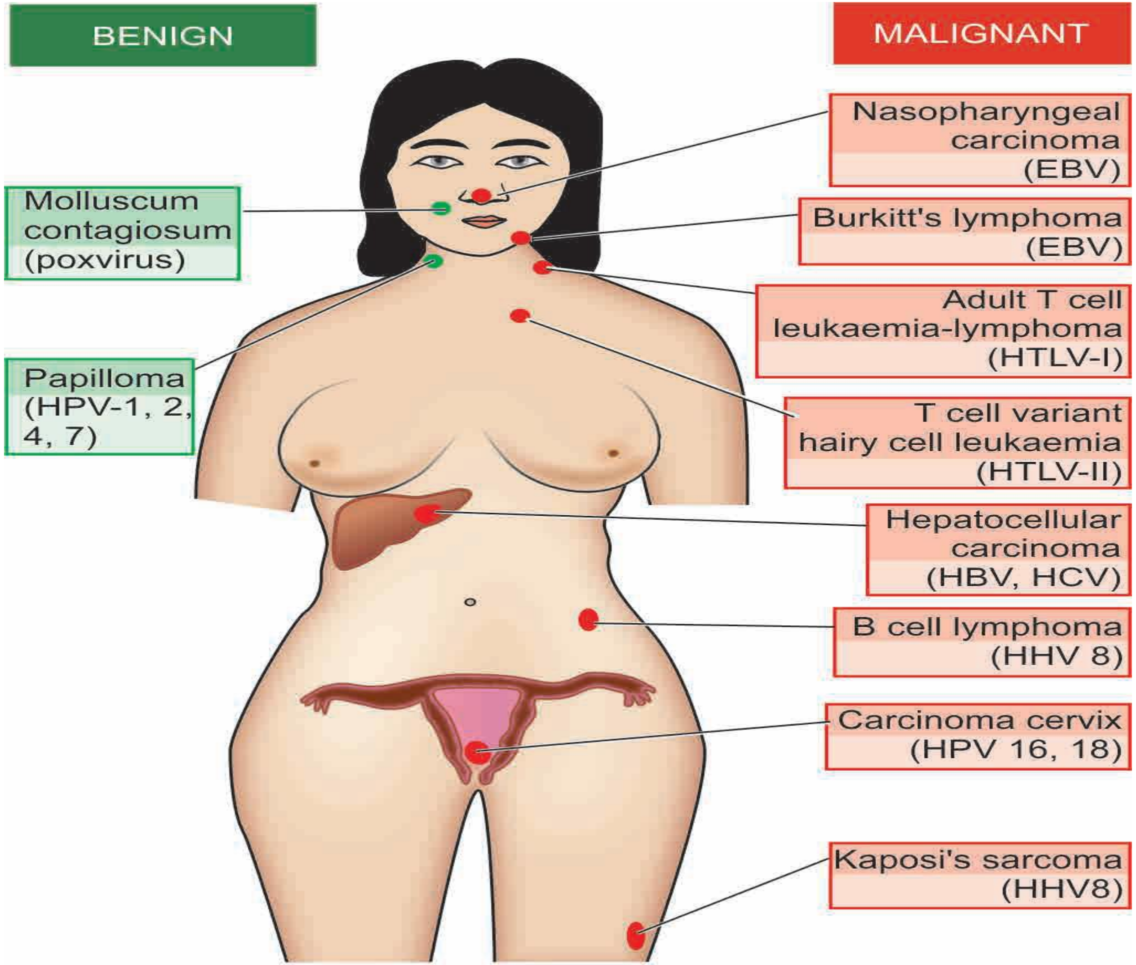


**BENIGN**

Molluscum contagiosum (poxvirus)

Papilloma (HPV-1, 2, 4, 7)

**MALIGNANT**

Nasopharyngeal carcinoma (EBV)

Burkitt's lymphoma (EBV)

Adult T cell leukaemia-lymphoma (HTLV-I)

T cell variant hairy cell leukaemia (HTLV-II)

Hepatocellular carcinoma (HBV, HCV)

B cell lymphoma (HHV 8)

Carcinoma cervix (HPV 16, 18)

Kaposi's sarcoma (HHV8)

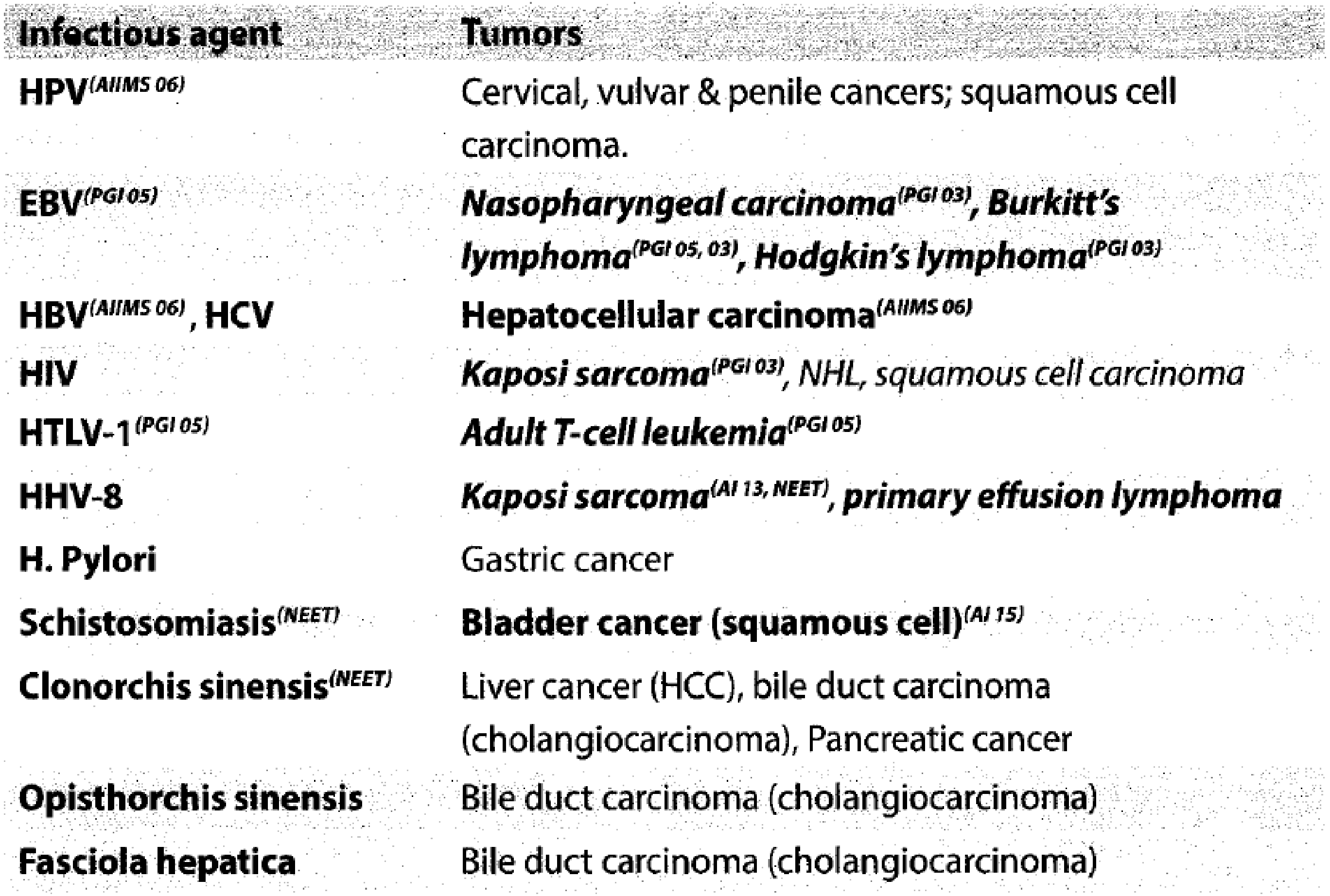
## Carcinogenic Viruses

### RNA viruses

- Human T cell leukemia virus-1 (HTLV-1)
- Hepatitis C virus (HCV)

### DNA viruses

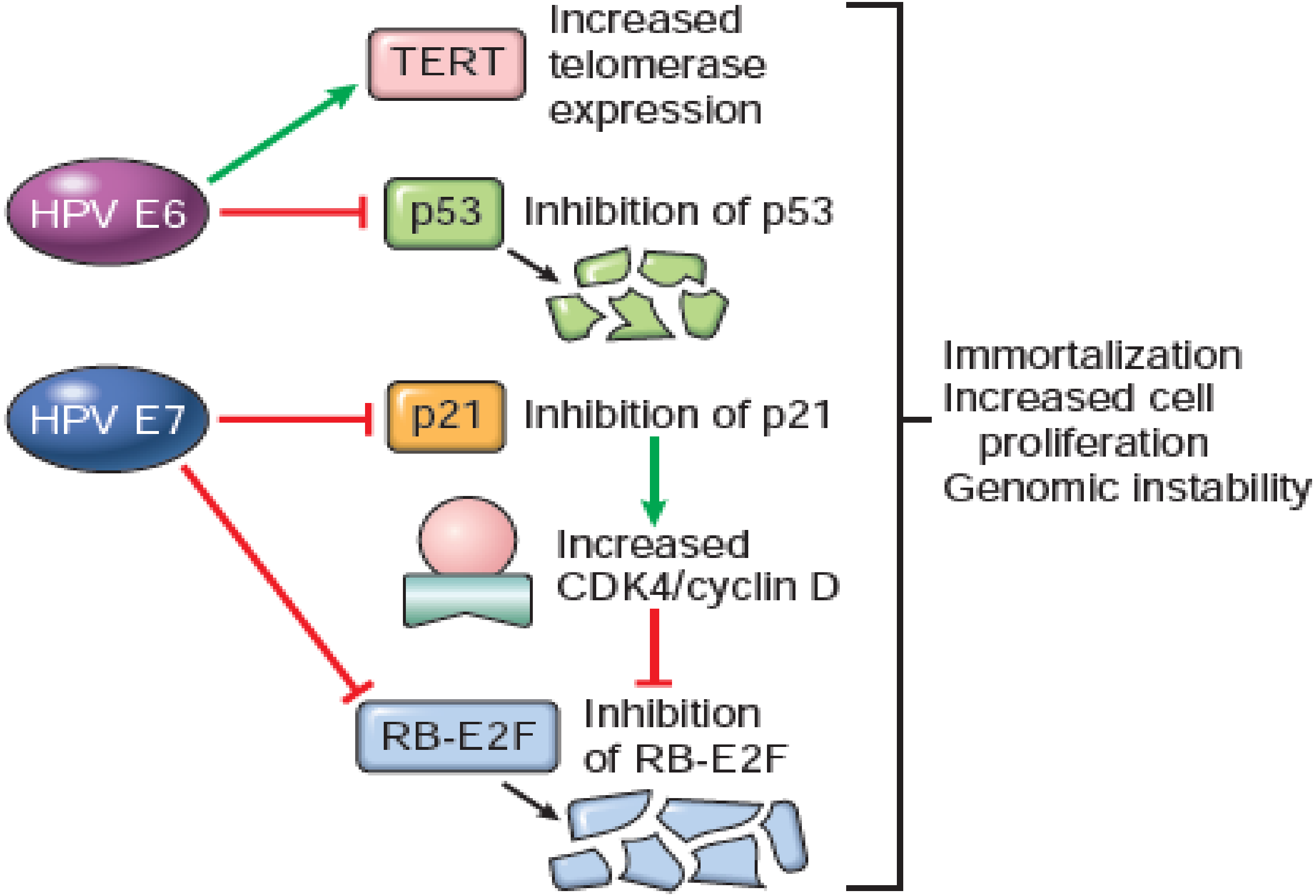
- Hepatitis B virus (HBV)
- Human herpes virus 8 (HHV8)
- Human papilloma virus (HPV)
- Epstein-Barr virus (EBV)



| Infectious agent | Tumors |
|---|---|
| **HPV(AIIMS 06)** | Cervical, vulvar & penile cancers; squamous cell carcinoma. |
| **EBV(PGI 05)** | ***Nasopharyngeal carcinoma(PGI 03), Burkitt's lymphoma(PGI 05, 03), Hodgkin's lymphoma(PGI 03)*** |
| **HBV(AIIMS 06), HCV** | **Hepatocellular carcinoma(AIIMS 06)** |
| **HIV** | ***Kaposi sarcoma(PGI 03)****, NHL, squamous cell carcinoma* |
| **HTLV-1(PGI 05)** | ***Adult T-cell leukemia(PGI 05)*** |
| **HHV-8** | ***Kaposi sarcoma(AI 13, NEET), primary effusion lymphoma*** |
| **H. Pylori** | Gastric cancer |
| **Schistosomiasis(NEET)** | **Bladder cancer (squamous cell)(AI 15)** |
| **Clonorchis sinensis(NEET)** | Liver cancer (HCC), bile duct carcinoma (cholangiocarcinoma), Pancreatic cancer |
| **Opisthorchis sinensis** | Bile duct carcinoma (cholangiocarcinoma) |
| **Fasciola hepatica** | Bile duct carcinoma (cholangiocarcinoma) |

# Human Papillomavirus (HPV)

- At least 70 genetically distinct types of HPV have been identified.
- **Low risk HPV (e.g., 1, 2, 4, and 7)** cause **benign** **squamous papillomas (warts)** in humans.
- **High-risk HPVs (e.g., types 16 and 18)** cause **squamous cell carcinomas of the cervix, anogenital region, and head and neck**
- These cancers are sexually transmitted diseases, caused by transmission of HPV


HPV E6
HPV E7
TERT
p53
p21
RB-E2F

Increased telomerase expression

Inhibition of p53

Inhibition of p21

Increased CDK4/cyclin D

Inhibition of RB-E2F

Immortalization
Increased cell proliferation
Genomic instability

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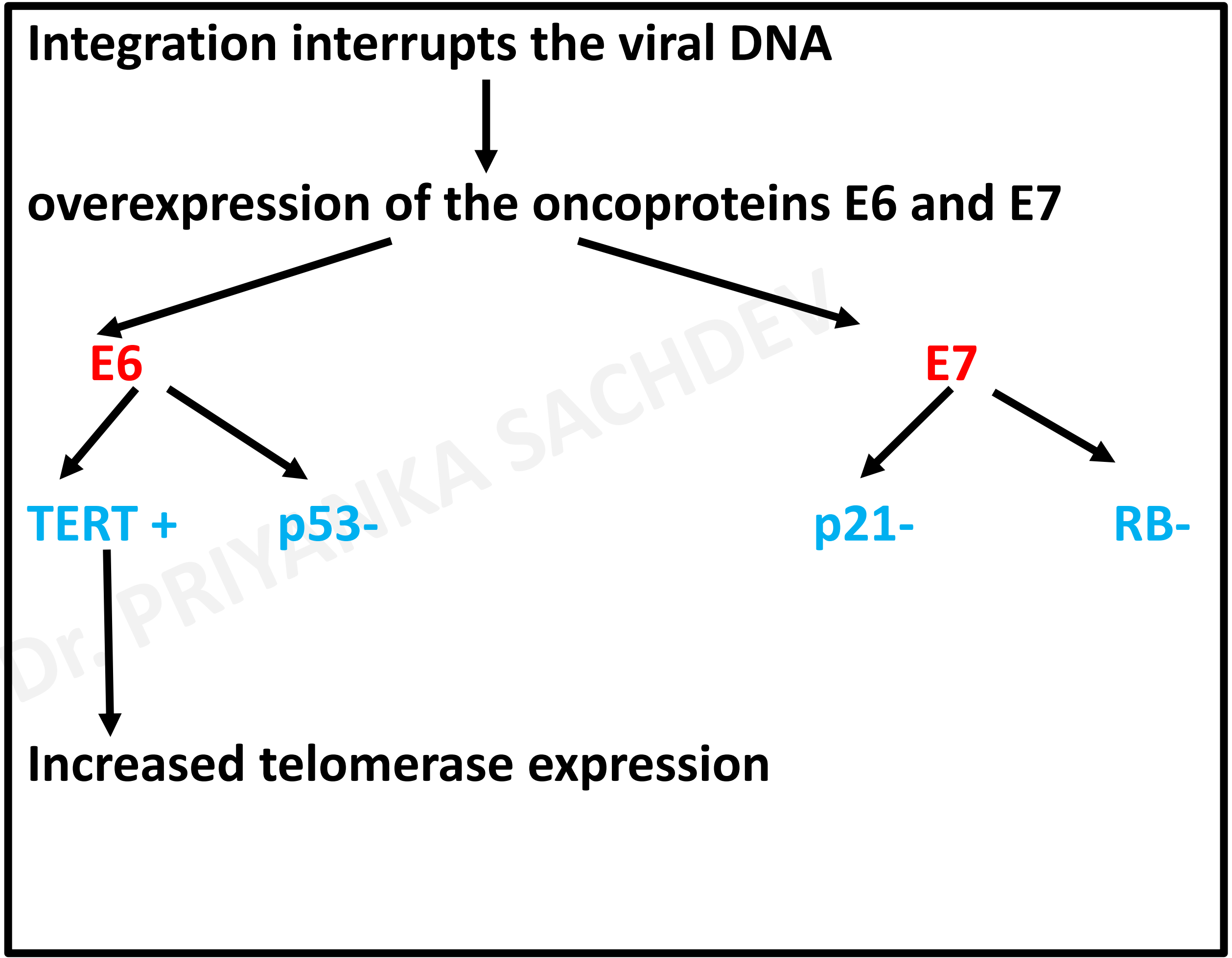


Integration interrupts the viral DNA

overexpression of the oncoproteins E6 and E7

E6

TERT +

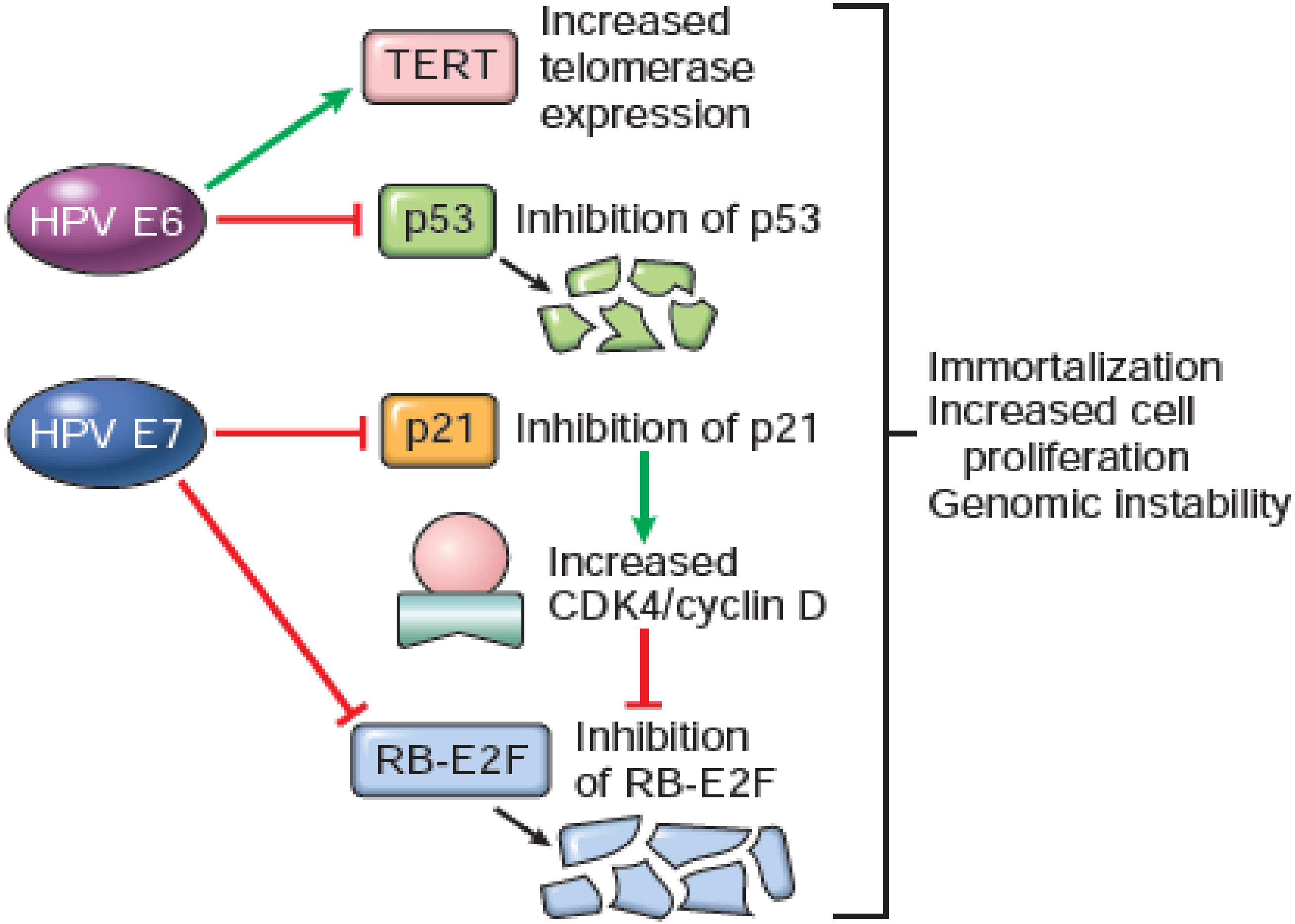
p53-

Increased telomerase expression

E7

p21-

RB-



HPV E6

HPV E7

TERT

Increased telomerase expression

p53

Inhibition of p53

p21

Inhibition of p21

Increased CDK4/cyclin D

RB-E2F

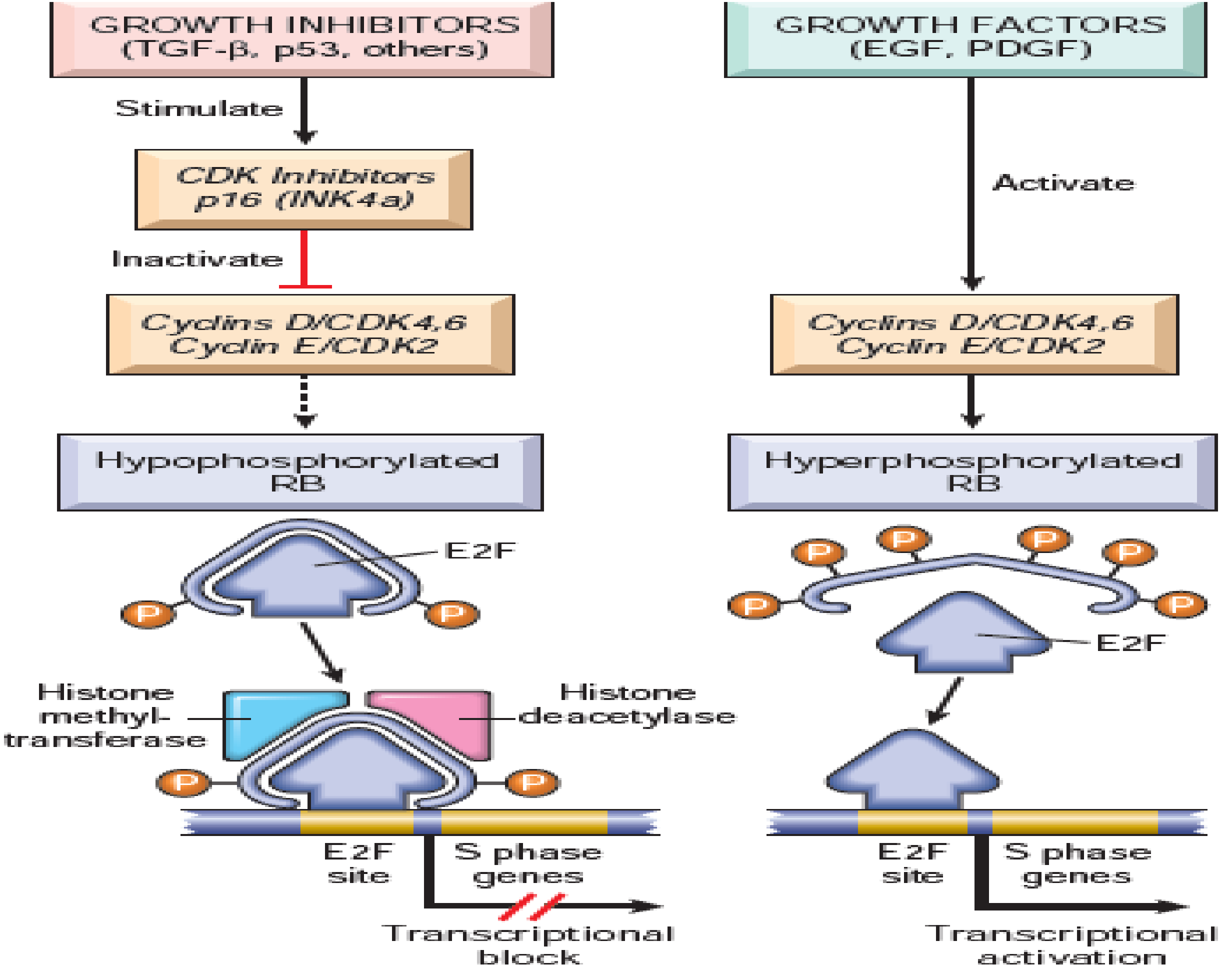
Inhibition of RB-E2F

Immortalization

Increased cell proliferation

Genomic instability

**Dr. PRIYANKA SACHDEV**



GROWTH INHIBITORS (TGF-β, p53, others)

Stimulate

*CDK Inhibitors p16 (INK4a)*

Inactivate

*Cyclins D/CDK4,6 Cyclin E/CDK2*

Hypophosphorylated RB

E2F
P
P
Histone methyl-transferase
Histone deacetylase
P
P
E2F site
S phase genes

Transcriptional block

GROWTH FACTORS (EGF, PDGF)

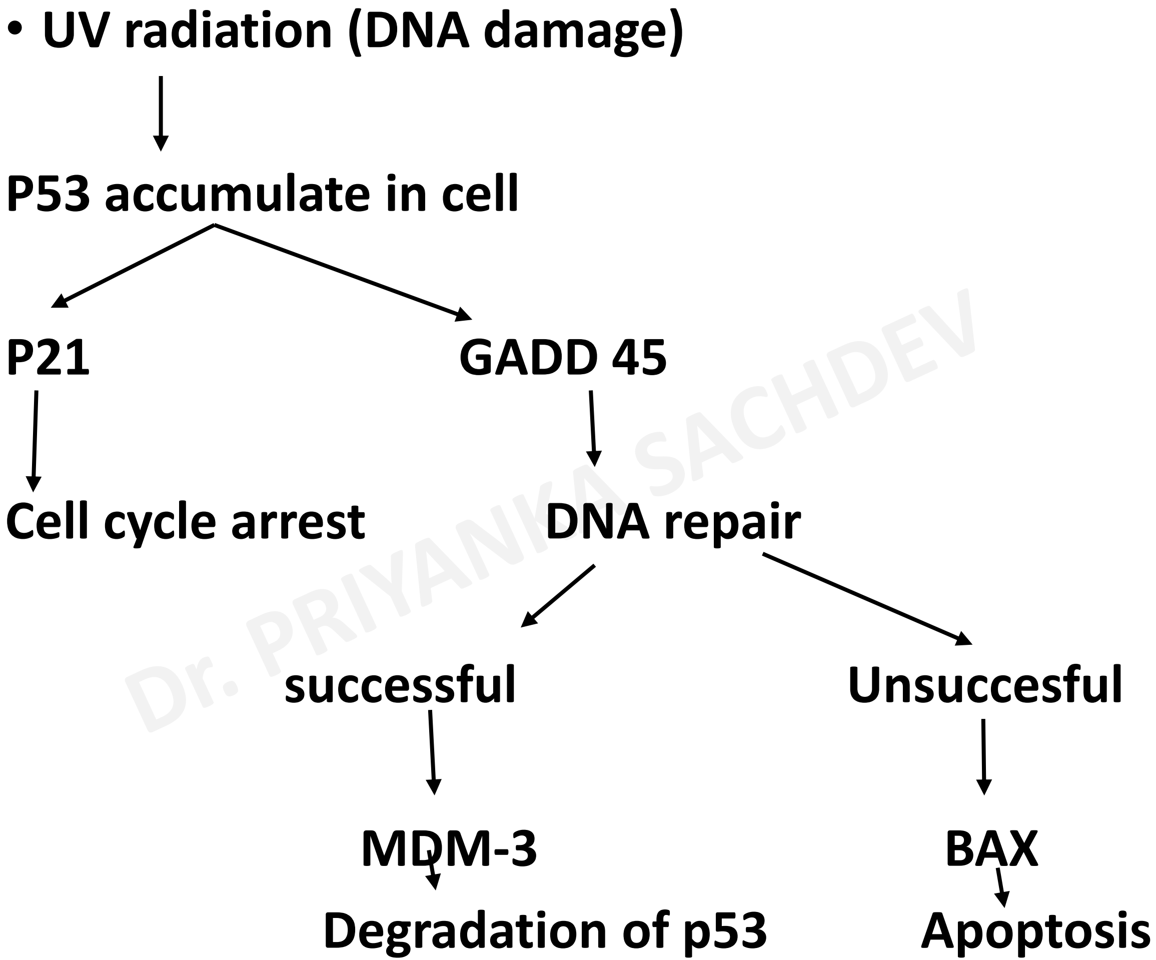
Activate

*Cyclins D/CDK4,6 Cyclin E/CDK2*

Hyperphosphorylated RB

P
P
P
P
P
P
E2F
E2F site
S phase genes

Transcriptional activation



- **UV radiation (DNA damage)**

**P53 accumulate in cell**

**P21**

**GADD 45**

**Cell cycle arrest**

**DNA repair**

**successful**

**Unsuccesful**

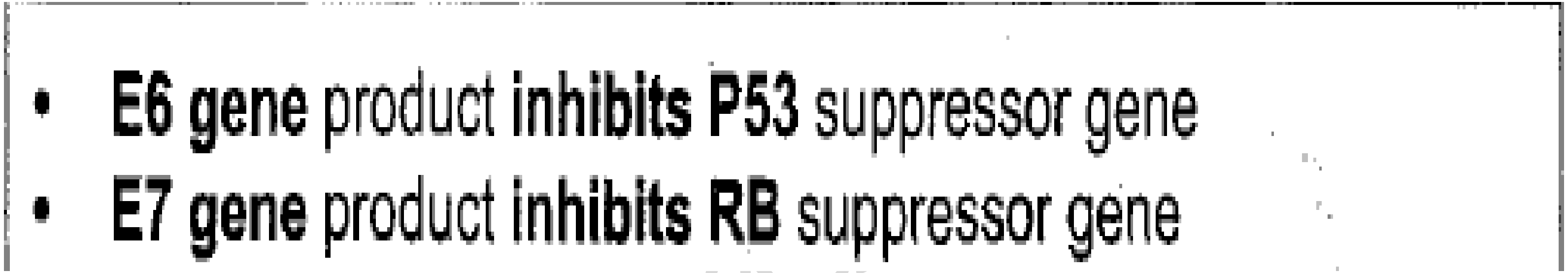
**MDM-3**

**Degradation of p53**

**BAX**

**Apoptosis**

# REMEMBER



- **E6 gene** product **inhibits P53** suppressor gene
- **E7 gene** product **inhibits RB** suppressor gene

# Epstein-Barr Virus (EBV)

- Burkitt lymphoma
- subset of Hodgkin lymphoma (lymphocyte depleted)
- Nasopharyngeal carcinoma
- Some gastric carcinomas
- T-cell lymphoma
- Natural killer (NK) cell lymphoma.

- Nasopharyngeal cancer is the only T cell malignancy amongst the cancers caused by EBV

**EBV causes infection of epithelial cells of oropharynx and B- cells because of the presence of CD21 molecule on the surface of these cells.**

↓

**LMP-1 gene present in the EBV integrate with human DNA**

↓

**Activation of NF-kB and JAK/STAT signaling pathways**

↓

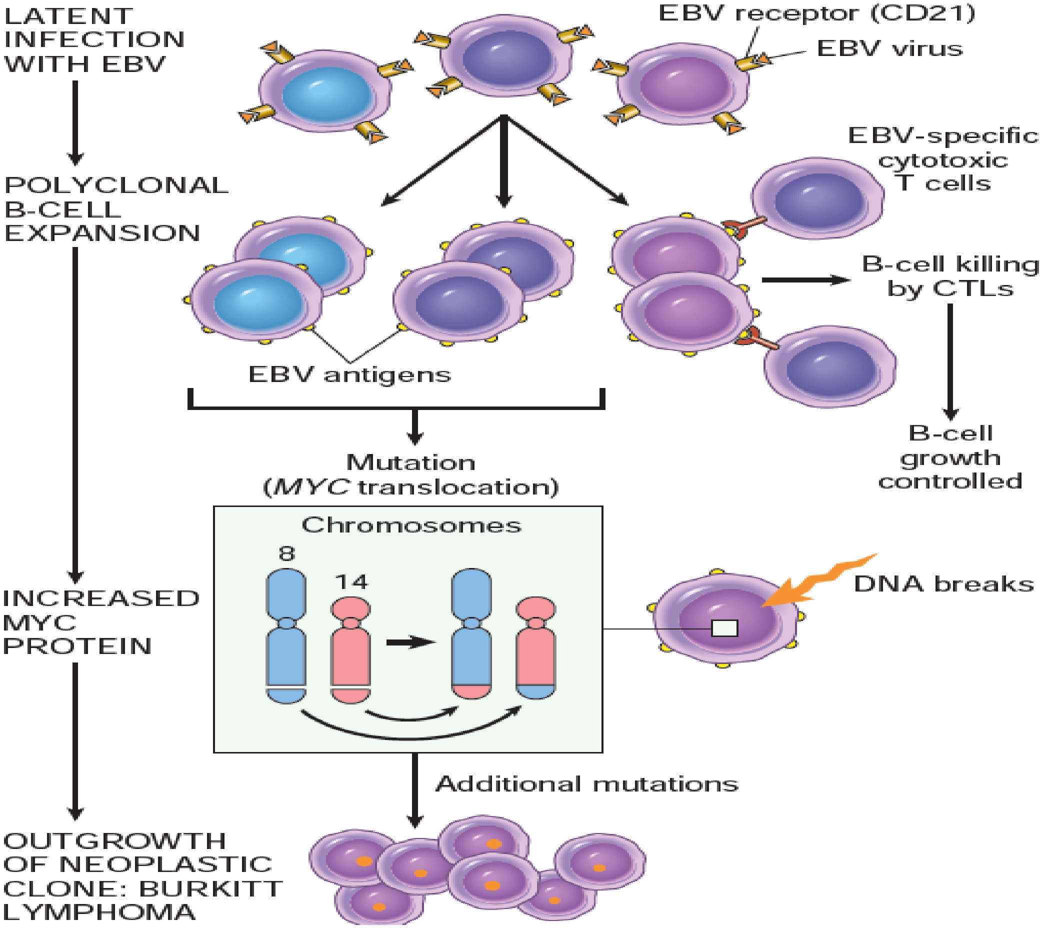
**promoting B-cell survival and proliferation (This increases the chances of B-cell lymphoma)**

↓

**Acquisition of t(8;14)translocation**

↓

**Burkitt lymphoma**



LATENT INFECTION WITH EBV

POLYCLONAL B-CELL EXPANSION

INCREASED MYC PROTEIN

OUTGROWTH OF NEOPLASTIC CLONE: BURKITT LYMPHOMA

EBV receptor (CD21)

EBV virus

EBV-specific cytotoxic T cells

B-cell killing by CTLs

B-cell growth controlled

EBV antigens

Mutation (*MYC* translocation)

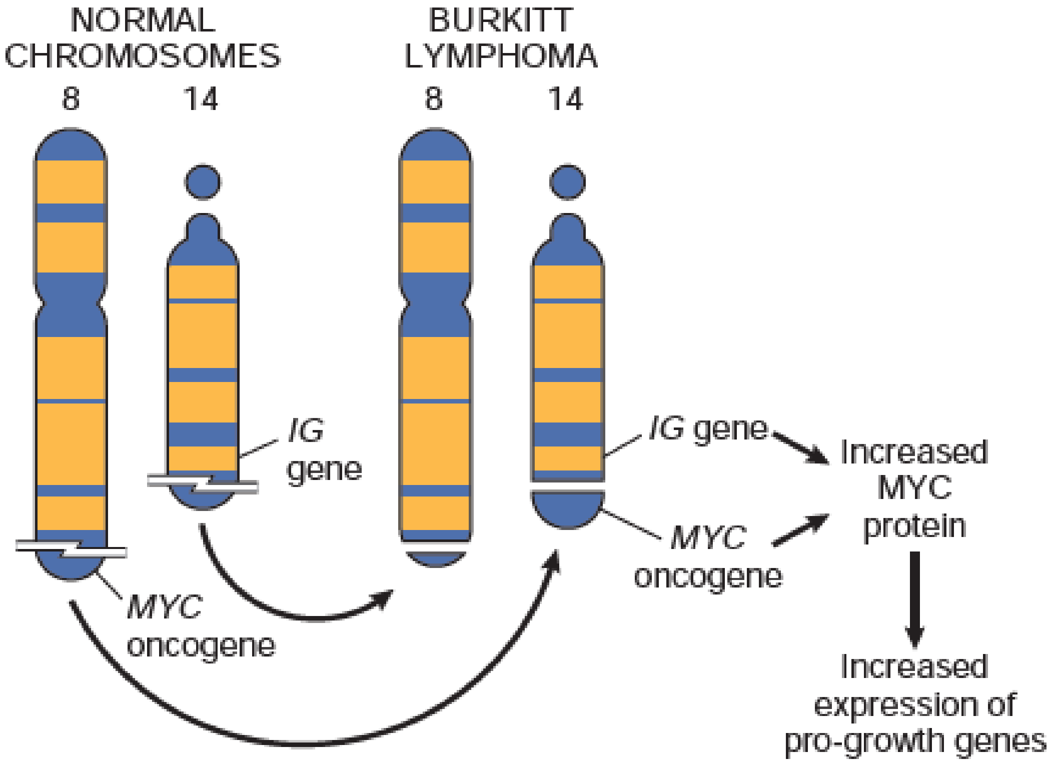
Chromosomes

8

14

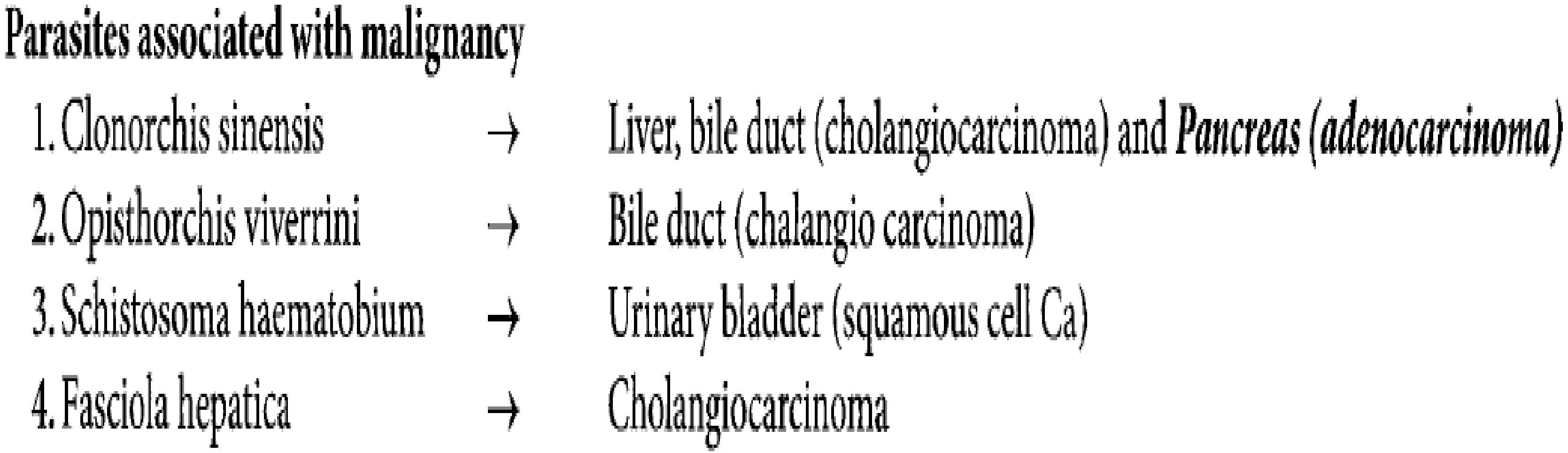
DNA breaks

Additional mutations


NORMAL CHROMOSOMES
8
14
BURKITT LYMPHOMA
8
14
*IG* gene
*MYC* oncogene
*IG* gene
*MYC* oncogene
Increased MYC protein
Increased expression of pro-growth genes

# REMEMBER

- In the case of Burkitt lymphoma, it seems that **EBV is not directly oncogenic**
- But by acting as **a polyclonal B-cell mitogen, it sets the stage for the acquisition of the (8;14) translocation** that ultimately produce a full-blown cancer.



**Parasites associated with malignancy**

1. Clonorchis sinensis → Liver, bile duct (cholangiocarcinoma) and ***Pancreas (adenocarcinoma)***
2. Opisthorchis viverrini → Bile duct (chalangio carcinoma)
3. Schistosoma haematobium → Urinary bladder (squamous cell Ca)
4. Fasciola hepatica → Cholangiocarcinoma

Dr. PRIYA

# BACTERIA

- H. pylori is the first bacterium classified as a carcinogen.
- H. pylori infection is implicated in the genesis of

**1. Gastric adenocarcinomas**

**2. Gastric lymphomas.**

FOLLOW US

- The gastric lymphomas are of **B-cell origin** and are called **MALT lymphomas** (marginal zone-associated lymphomas) because the transformed B cells normally reside in the marginal zones of lymphoid follicles.

- H. pylori infection results in the formation of H. pylori-reactive T cells, which cause polyclonal B-cell proliferations.

- The MALT lymphoma is associated with **t(11;18)** translocation.

# 3 TYPES→

A. Chemical carcinogens
B. Physical carcinogens
C. Biologic carcinogens

# POLLS 3

Scan or Click to watch Neoplasia E01

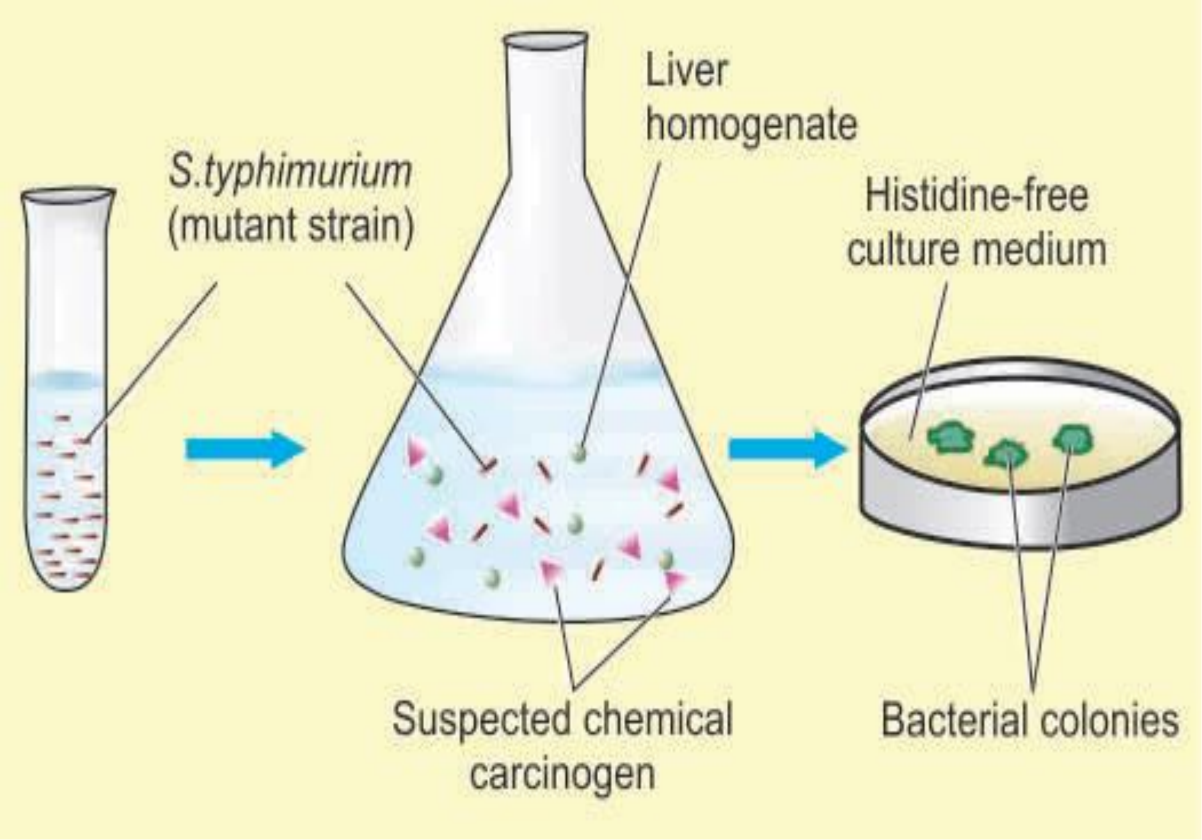
Scan or Click to watch Neoplasia E02

# A simple bacterial test for mutagenic carcinogens is-

a) Ames test
b) Redox test
c) Bacteriophage
d) Gene splicing

Dr. Pr

# A


*S.typhimurium*
(mutant strain)
Liver
homogenate
Histidine-free
culture medium
Suspected chemical
carcinogen
Bacterial colonies

**Radiation is most commonly associated with which of the following cancer?**

a) Leukemia
b) Lymphoma
c) Lung carcinoma
d) Osteoblastoma

Dr.

# A

# Virus causing hemopoietic carcinoma are -

- a. EBV
- b. HHV-8
- c. CMV
- d. Kaposi sarcoma

# A

***H. pylori*** **infection is associated with development of which malignancy:**

(a) MALTomas
(b) Atherosclerosis
(c) Sarcoma
(d) Gastrointestinal stromal tumor (GIST)

# A

**Helicobacter pylori infection is associated with all of the following conditions, except:**

(a) Peptic ulcer disease

(b) Gastric adenocarcinoma

(c) B cell lymphoma

(d) Burkitt's lymphoma

# D

# BACTERIA

- H. pylori is the first bacterium classified as a carcinogen.
- H. pylori infection is implicated in the genesis of

1. **Gastric adenocarcinomas**
2. **Gastric lymphomas.**

- The gastric lymphomas are of **B-cell origin** and are called **MALT lymphomas** (marginal zone-associated lymphomas) because the transformed B cells normally reside in the marginal zones of lymphoid follicles.

- H. pylori infection results in the formation of H. pylori-reactive T cells, which cause polyclonal B-cell proliferations.

- The MALT lymphoma is associated with **t(11;18)** translocation.

**Tumors associated with organisms are all except:**

(a) Hepatocellular cancer
(b) Non-small Cell Carcinoma of Lung
(c) Gastric cancer
(d) Nasopharyngeal cancer

Dr. PRIYAN

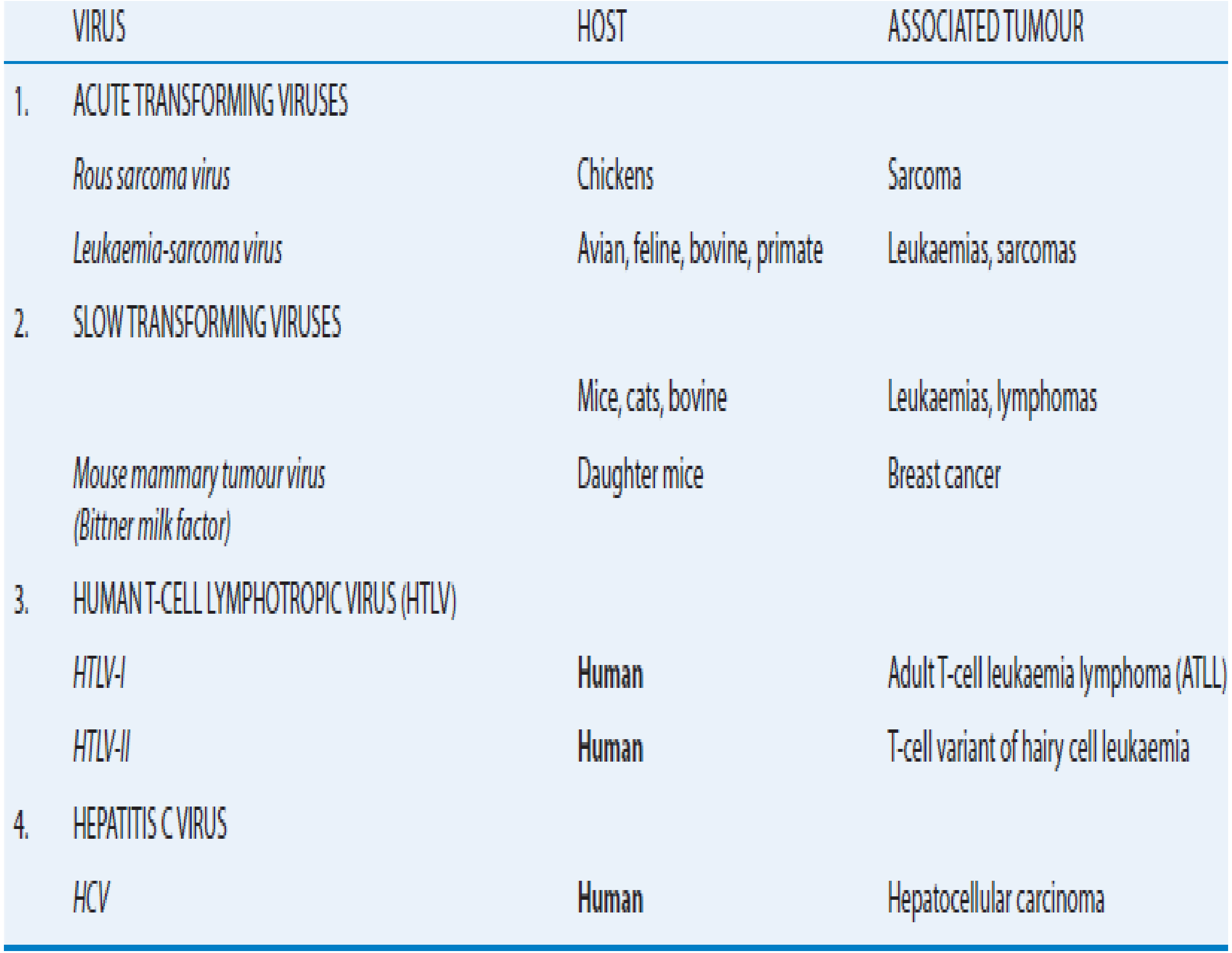
# B

**Which of the following is an oncogenic RNA virus?**

(a) Hepatitis B virus
(b) Human papilloma virus
(c) Epstein Barr virus
(d) Hepatitis C virus

Dr. PRIYAN

# D



| | VIRUS | HOST | ASSOCIATED TUMOUR |
|---|---|---|---|
| 1. | ACUTE TRANSFORMING VIRUSES | | |
| | *Rous sarcoma virus* | Chickens | Sarcoma |
| | *Leukaemia-sarcoma virus* | Avian, feline, bovine, primate | Leukaemias, sarcomas |
| 2. | SLOW TRANSFORMING VIRUSES | | |
| | | Mice, cats, bovine | Leukaemias, lymphomas |
| | *Mouse mammary tumour virus (Bittner milk factor)* | Daughter mice | Breast cancer |
| 3. | HUMAN T-CELL LYMPHOTROPIC VIRUS (HTLV) | | |
| | *HTLV-I* | **Human** | Adult T-cell leukaemia lymphoma (ATLL) |
| | *HTLV-II* | **Human** | T-cell variant of hairy cell leukaemia |
| 4. | HEPATITIS C VIRUS | | |
| | *HCV* | **Human** | Hepatocellular carcinoma |

)

**LMP-1 gene plays a role in oncogenesis induced by:**

(a) Human T cell leukemia virus type I
(b) Hepatitis B virus
(c) Epstein-Barr virus
(d) Human papilloma virus

Dr. PRIYA

# c

**Skin cancers develop due to sunlight exposure induced by:**

(a) UVA rays
(b) UVB rays
(c) UVC rays
(d) UVD rays

Dr. PRIYA

# B

- has three subtypes

1. **UV-A** is 320-400 nm
2. **UV-B** is 280- 320 nm
3. **UV-C** is 200 - 280 nm

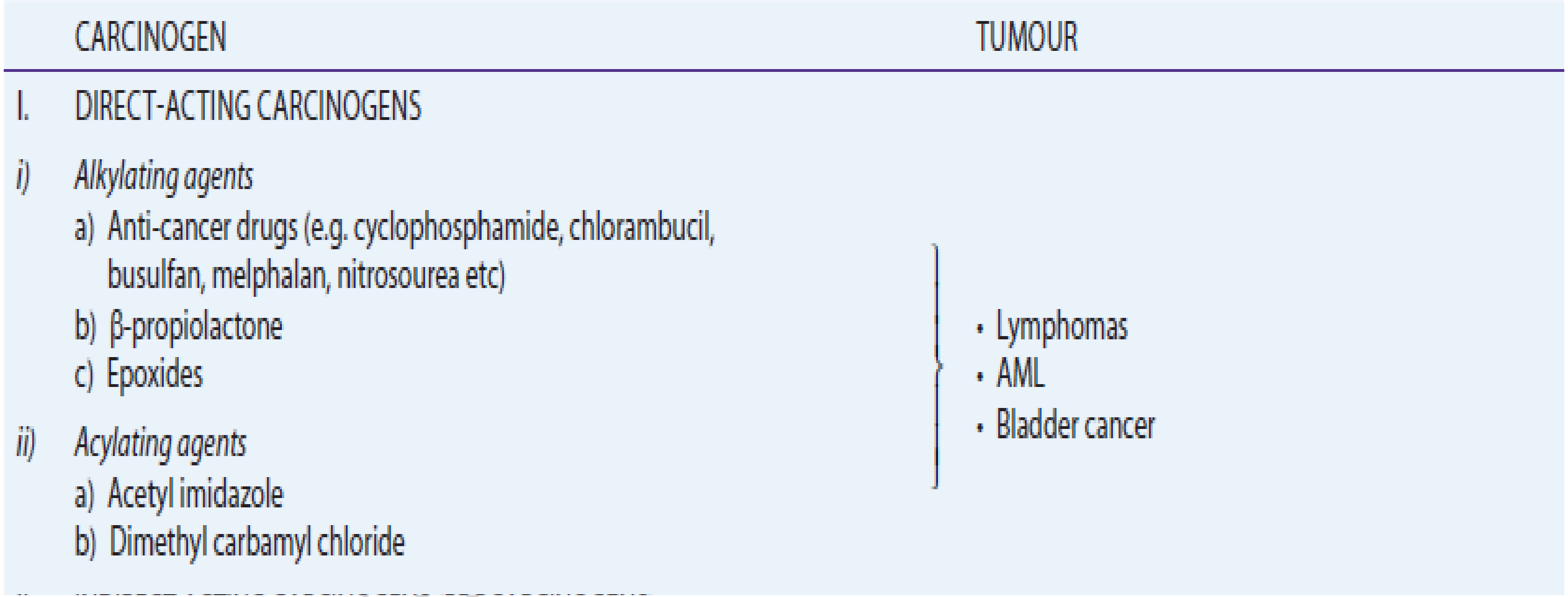
- **UV-C** gets filtered by ozone layer
- **UV-B** is the most carcinogenic UV ray to reach the earth

(**UV-B** is Bad for humans as it causes cancers)

**Workers exposed to polyvinyl chloride may develop following liver malignancy:**

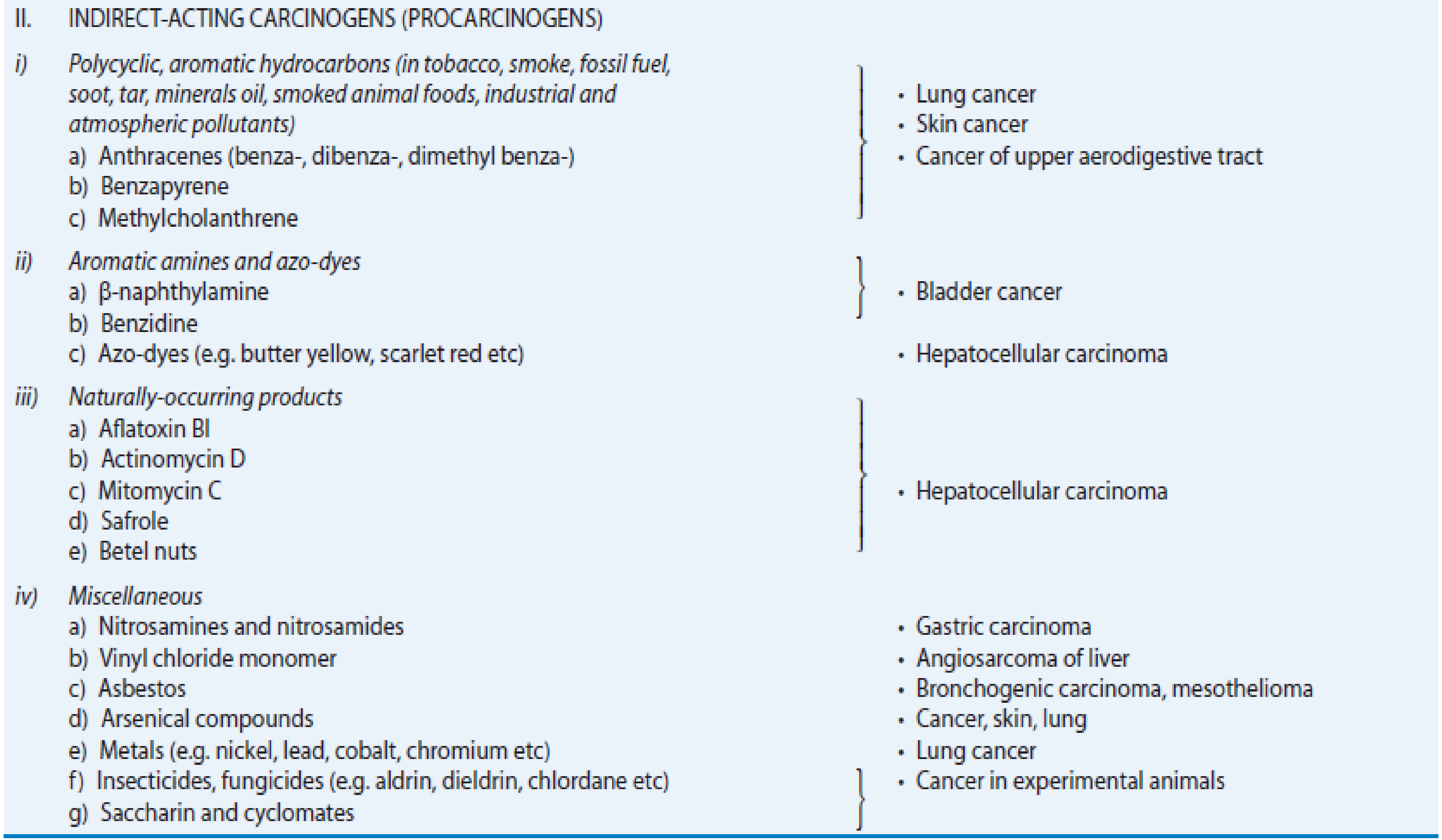
(a) Cholangiocarcinoma
(b) Fibrolamellar carcinoma
(c) Angiosarcoma
(d) All of the above

# c



| CARCINOGEN | TUMOUR |
|---|---|
| I. DIRECT-ACTING CARCINOGENS | |
| *i) Alkylating agents* | |
| a) Anti-cancer drugs (e.g. cyclophosphamide, chlorambucil, busulfan, melphalan, nitrosourea etc) | • Lymphomas<br>• AML<br>• Bladder cancer |
| b) β-propiolactone | |
| c) Epoxides | |
| *ii) Acylating agents* | |
| a) Acetyl imidazole | |
| b) Dimethyl carbamyl chloride | |

Dr. P



| | | |
|---|---|---|
| II. | INDIRECT-ACTING CARCINOGENS (PROCARCINOGENS) | |
| *i)* | *Polycyclic, aromatic hydrocarbons (in tobacco, smoke, fossil fuel, soot, tar, minerals oil, smoked animal foods, industrial and atmospheric pollutants)* | • Lung cancer<br>• Skin cancer<br>• Cancer of upper aerodigestive tract |
| | a) Anthracenes (benza-, dibenza-, dimethyl benza-) | |
| | b) Benzapyrene | |
| | c) Methylcholanthrene | |
| *ii)* | *Aromatic amines and azo-dyes* | |
| | a) β-naphthylamine | • Bladder cancer |
| | b) Benzidine | |
| | c) Azo-dyes (e.g. butter yellow, scarlet red etc) | • Hepatocellular carcinoma |
| *iii)* | *Naturally-occurring products* | |
| | a) Aflatoxin BI | • Hepatocellular carcinoma |
| | b) Actinomycin D | |
| | c) Mitomycin C | |
| | d) Safrole | |
| | e) Betel nuts | |
| *iv)* | *Miscellaneous* | |
| | a) Nitrosamines and nitrosamides | • Gastric carcinoma |
| | b) Vinyl chloride monomer | • Angiosarcoma of liver |
| | c) Asbestos | • Bronchogenic carcinoma, mesothelioma |
| | d) Arsenical compounds | • Cancer, skin, lung |
| | e) Metals (e.g. nickel, lead, cobalt, chromium etc) | • Lung cancer |
| | f) Insecticides, fungicides (e.g. aldrin, dieldrin, chlordane etc) | • Cancer in experimental animals |
| | g) Saccharin and cyclomates | |

**Which among the following is not a neoplastic virus:**

(a) Cytomegalovirus
(b) Hepatitis B virus
(c) Human papilloma virus
(d) All of these

Dr. PRIYANK

# A

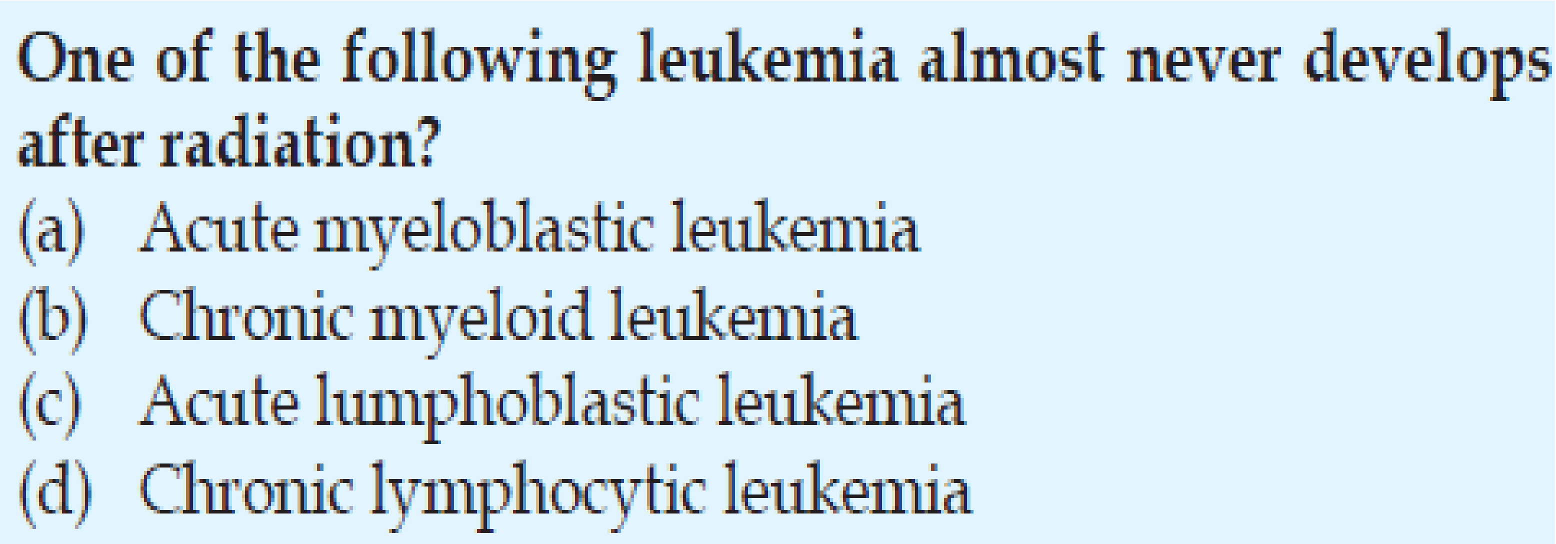
## Carcinogenic Viruses

### RNA viruses

- Human T cell leukemia virus-1 (HTLV-1)
- Hepatitis C virus (HCV)

### DNA viruses

- Hepatitis B virus (HBV)
- Human herpes virus 8 (HHV8)
- Human papilloma virus (HPV)
- Epstein-Barr virus (EBV)



**One of the following leukemia almost never develops after radiation?**

(a) Acute myeloblastic leukemia
(b) Chronic myeloid leukemia
(c) Acute lumphoblastic leukemia
(d) Chronic lymphocytic leukemia

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# D

# REMEMBER

- **CLL** is the only leukemia NOT associated with ionizing radiation exposure.

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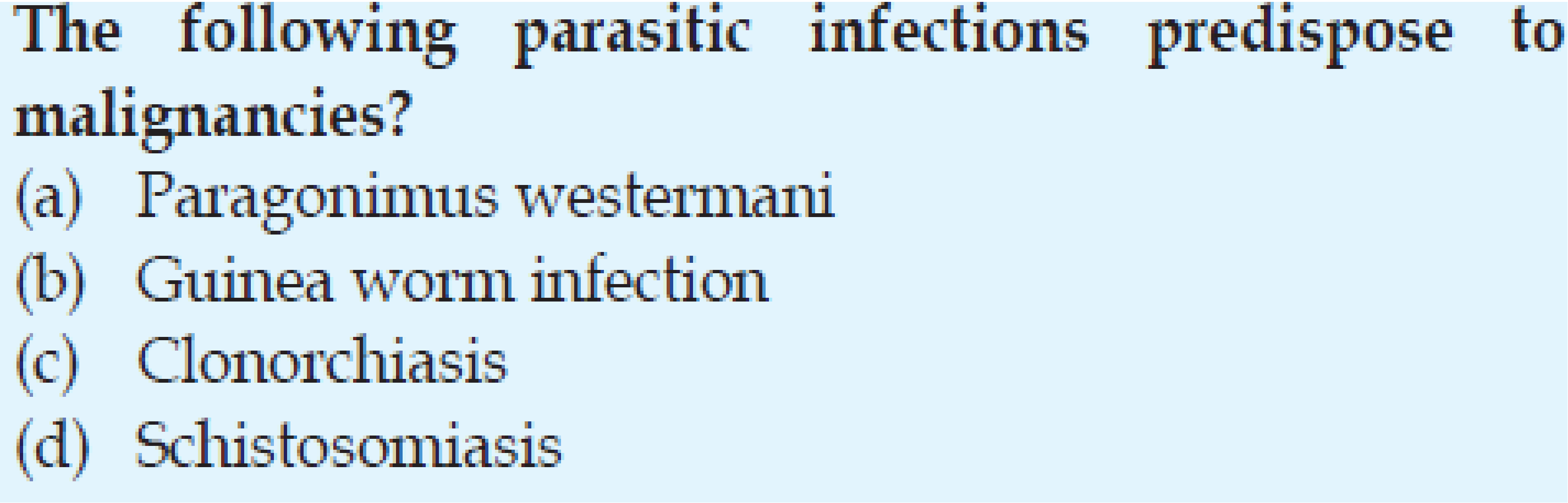

**The following parasitic infections predispose to malignancies?**

(a) Paragonimus westermani

(b) Guinea worm infection

(c) Clonorchiasis

(d) Schistosomiasis

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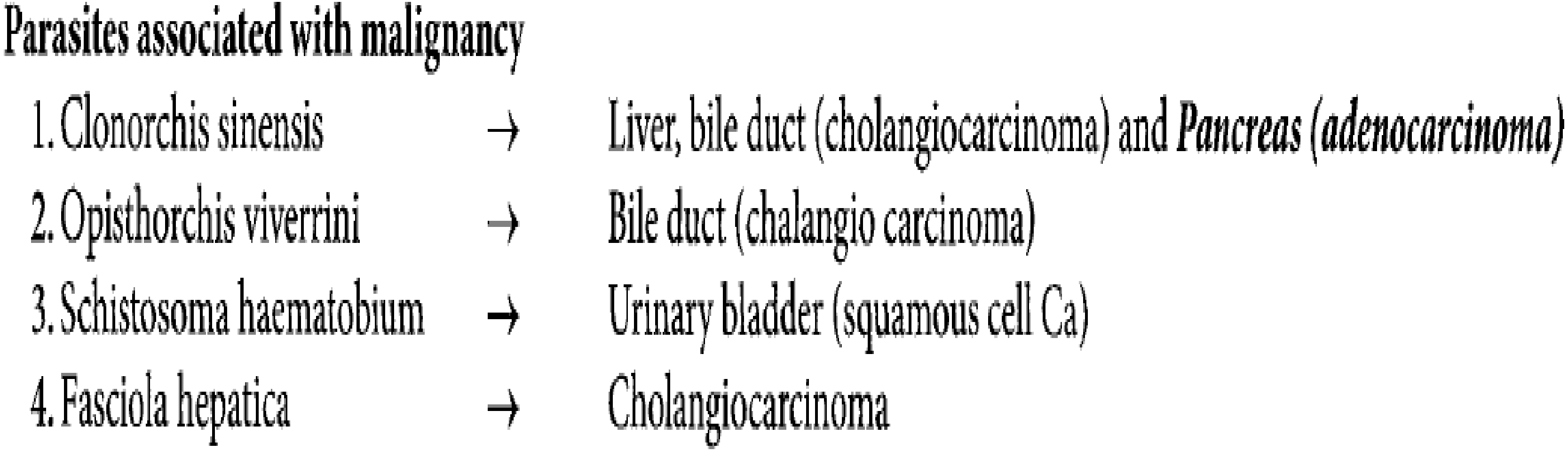
# c



**Parasites associated with malignancy**

1. Clonorchis sinensis → Liver, bile duct (cholangiocarcinoma) and ***Pancreas (adenocarcinoma)***
2. Opisthorchis viverrini → Bile duct (chalangio carcinoma)
3. Schistosoma haematobium → Urinary bladder (squamous cell Ca)
4. Fasciola hepatica → Cholangiocarcinoma

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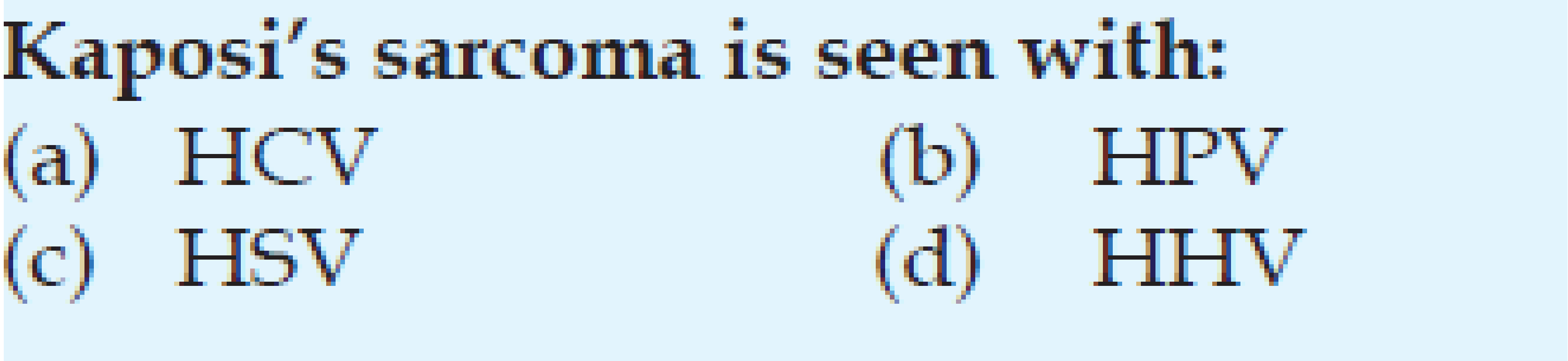
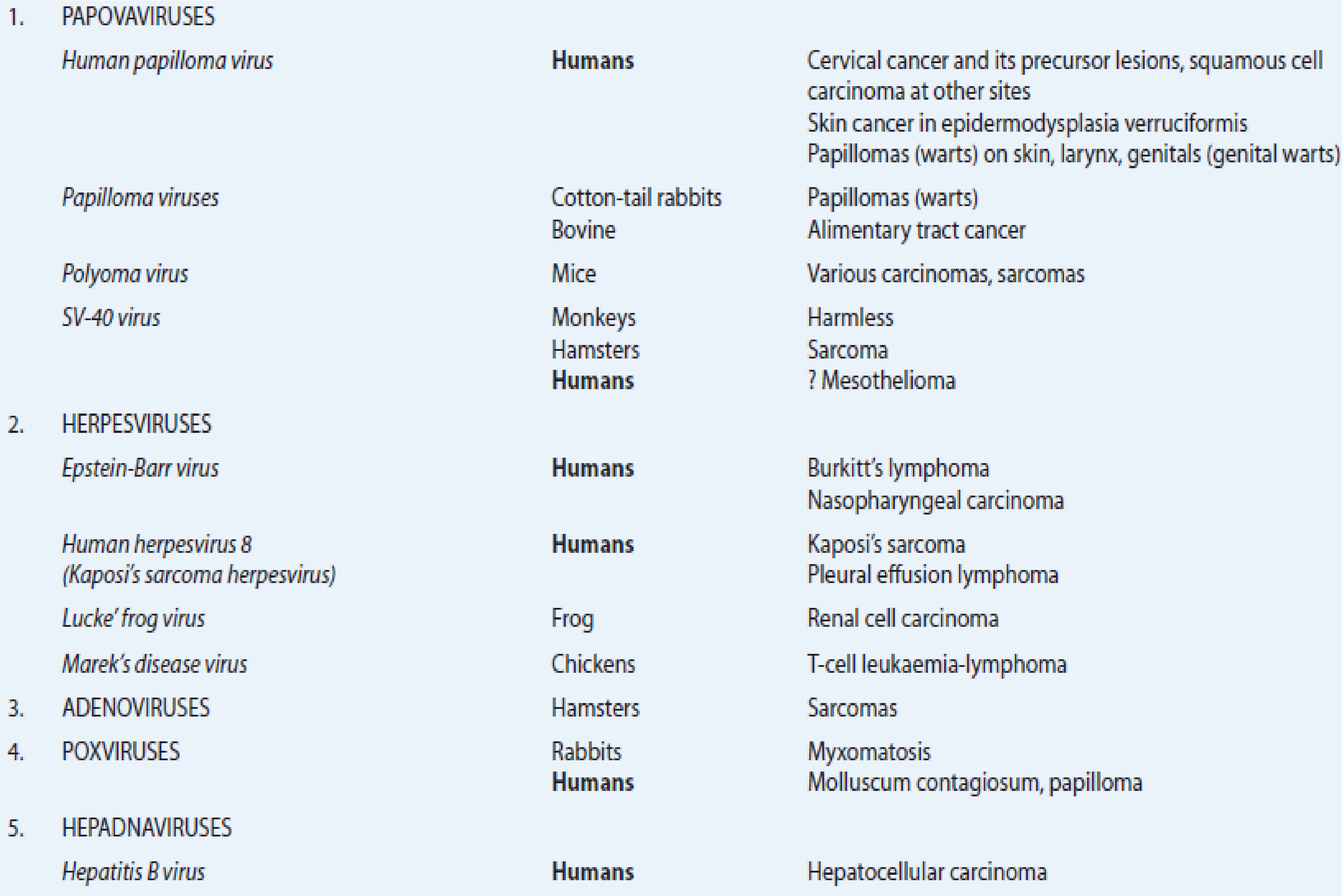


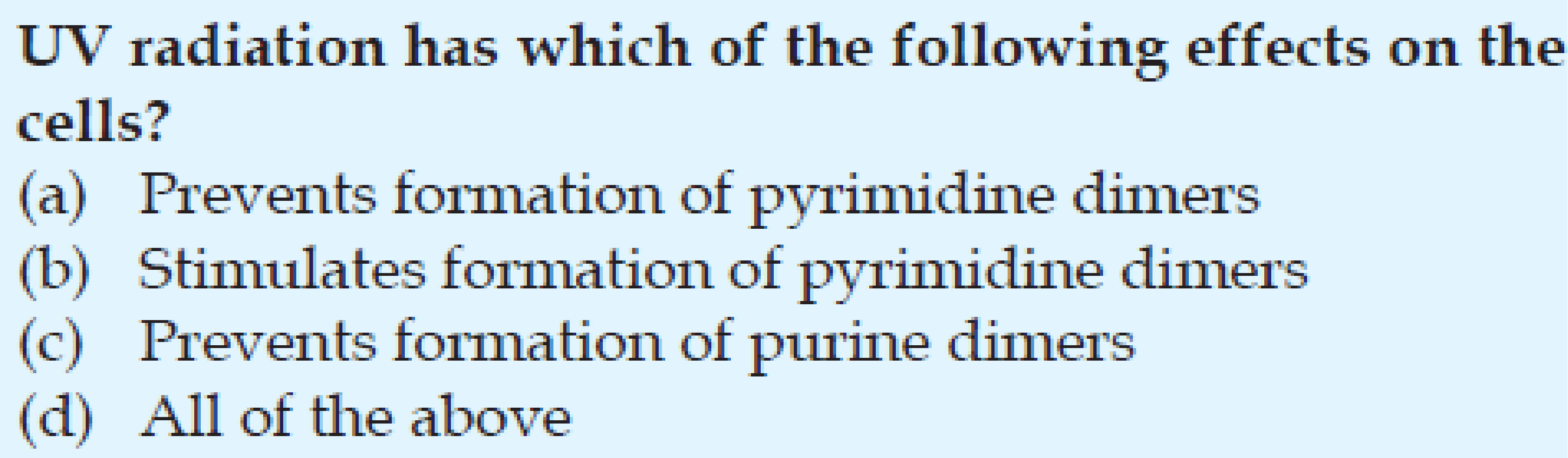
**Kaposi's sarcoma is seen with:**

(a) HCV
(b) HPV
(c) HSV
(d) HHV

# D



| | | | |
|---|---|---|---|
| 1. | PAPOVAVIRUSES | | |
| | *Human papilloma virus* | **Humans** | Cervical cancer and its precursor lesions, squamous cell carcinoma at other sites<br>Skin cancer in epidermodysplasia verruciformis<br>Papillomas (warts) on skin, larynx, genitals (genital warts) |
| | *Papilloma viruses* | Cotton-tail rabbits | Papillomas (warts) |
| | | Bovine | Alimentary tract cancer |
| | *Polyoma virus* | Mice | Various carcinomas, sarcomas |
| | *SV-40 virus* | Monkeys | Harmless |
| | | Hamsters | Sarcoma |
| | | **Humans** | ? Mesothelioma |
| 2. | HERPESVIRUSES | | |
| | *Epstein-Barr virus* | **Humans** | Burkitt's lymphoma<br>Nasopharyngeal carcinoma |
| | *Human herpesvirus 8 (Kaposi's sarcoma herpesvirus)* | **Humans** | Kaposi's sarcoma<br>Pleural effusion lymphoma |
| | *Lucke' frog virus* | Frog | Renal cell carcinoma |
| | *Marek's disease virus* | Chickens | T-cell leukaemia-lymphoma |
| 3. | ADENOVIRUSES | Hamsters | Sarcomas |
| 4. | POXVIRUSES | Rabbits | Myxomatosis |
| | | **Humans** | Molluscum contagiosum, papilloma |
| 5. | HEPADNAVIRUSES | | |
| | *Hepatitis B virus* | **Humans** | Hepatocellular carcinoma |



**UV radiation has which of the following effects on the cells?**

(a) Prevents formation of pyrimidine dimers
(b) Stimulates formation of pyrimidine dimers
(c) Prevents formation of purine dimers
(d) All of the above

# B

# Mechanism

Exposure to UV rays

↓

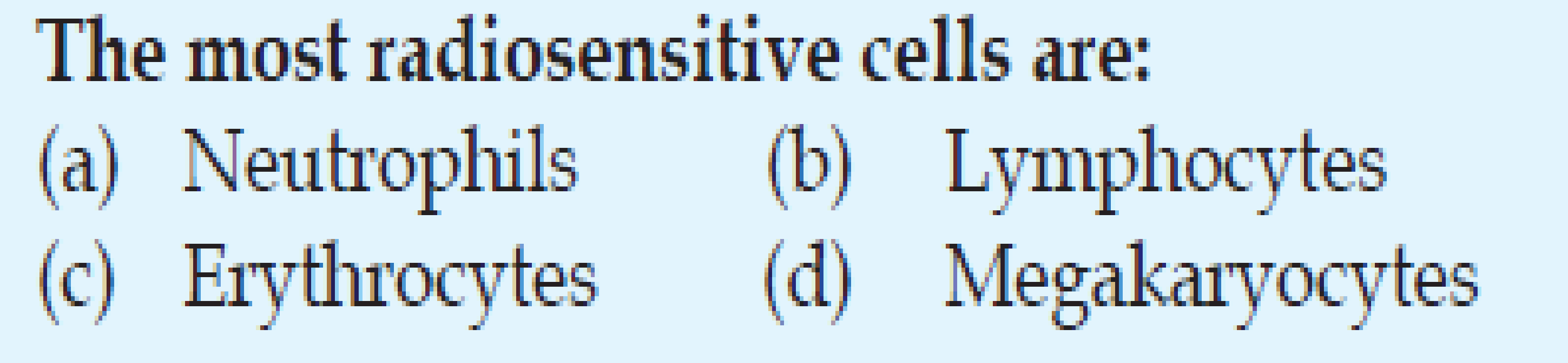
Pyrimidine dimers in DNA

↓

Mutation in oncogenes and tumor suppressor genes

↓

Cancer



**The most radiosensitive cells are:**

(a) Neutrophils
(b) Lymphocytes
(c) Erythrocytes
(d) Megakaryocytes

# B

# REMEMBER

- The **most radiosensitive** cell in the **blood** is the **lymphocytes**
- The **least radiosensitive** cell in the **blood** is the **platelets**
- **DNA** is the most sensitive intracellular organelle to radiation.

# CLINICAL FEATURES

# CLINICAL FEATURES

- A. LOCAL EFFECTS
- B. SYSTEMIC MANIFESTATIONS

# A. LOCAL EFFECTS

- **Compression**→ Some benign tumours due to their critical location, have more serious consequences e.g. pituitary adenoma
- **Mechanical obstruction** Benign and malignant tumours in the gut may produce intestinal obstruction.
- **Tissue destruction** Malignant tumours infiltrate and destroy the vital structures
- **Infarction, ulceration, haemorrhage**

# B. SYSTEMIC MANIFESTATIONS

1. Cacer cachexia
2. Fever
3. Tumour lysis syndrome
4. Paraneoplastic syndrome

# 1.CANCER CACHEXIA

- Due to **anorexia and increased nutritional demands of the tumour.**
- Certain cytokines such as **tumour necrosis factor a (TNF-a), IL-1 and INF-g** play a contributory role in cachexia

# 2. FEVER

- Exact mechanism of tumour-associated fever is not known
- Probably the tumour cells themselves elaborate pyrogens.

# 3. TUMOUR LYSIS SYNDROME

- Caused by **extensive destruction of a large number of rapidly proliferating tumour cells**

# Tumor lysis syndrome is associated with

1. Burkitt lymphoma
2. Acute lymphoblastic leukemia (ALL)
3. Chronic tumors (CLL)
4. uncommonly solid tumors

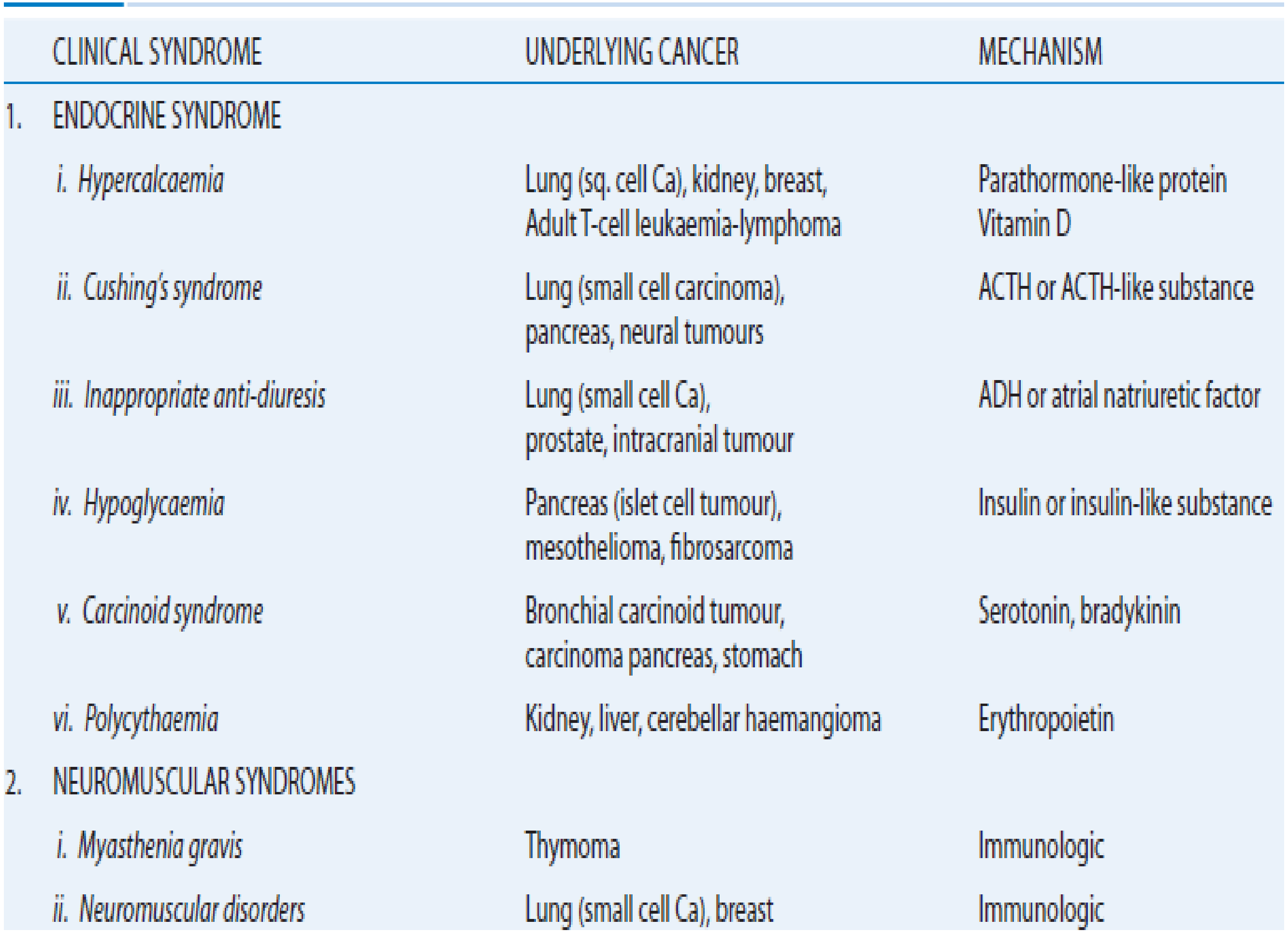
- Characterised by →

1. **Hyperuricaemia**(due to increased turnover of nucleic acids).Hyperuricemia can cause uric acid precipitation in the kidney causing acute renal failure.
2. **Hyperkalaemia** (due to release of the most abundant intracellular cation potassium)
3. **Hyperphosphataemia** (due to release of intracellular phosphate)
4. **Hypocalcaemia** (due to complexing of calcium with the elevated phosphate)

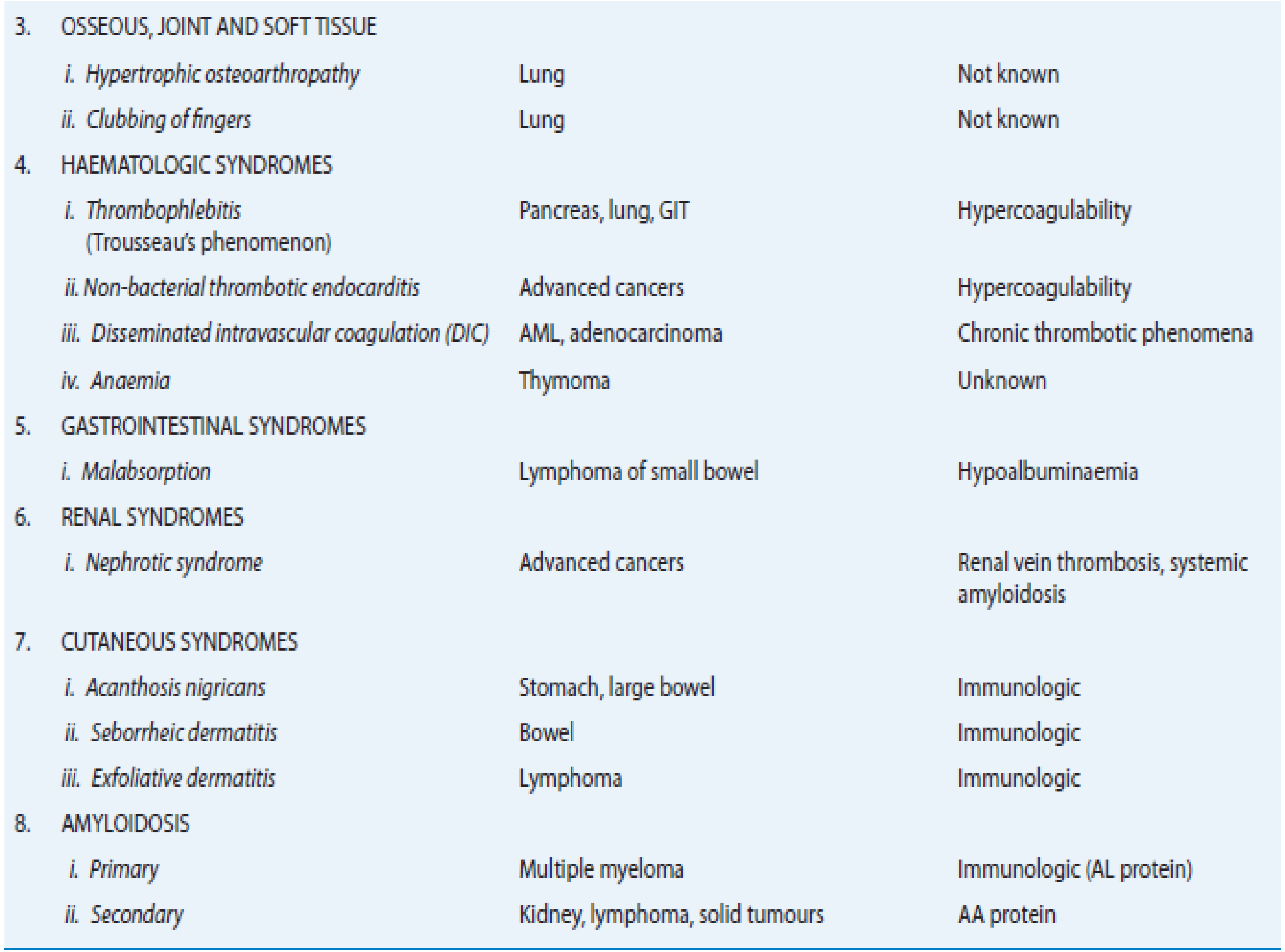
# 4. PARANEOPLASTIC SYNDROME

- A group of conditions developing in patients with advanced cancer **which are neither explained by direct and distant spread of the tumour**

- About 10 to 15% of the patients with advanced cancer develop paraneoplastic syndromes
- Sometimes PNS may be the **earliest manifestation of a latent cancer.**



| | CLINICAL SYNDROME | UNDERLYING CANCER | MECHANISM |
|---|---|---|---|
| 1. | ENDOCRINE SYNDROME | | |
| | *i. Hypercalcaemia* | Lung (sq. cell Ca), kidney, breast,<br>Adult T-cell leukaemia-lymphoma | Parathormone-like protein<br>Vitamin D |
| | *ii. Cushing's syndrome* | Lung (small cell carcinoma), pancreas, neural tumours | ACTH or ACTH-like substance |
| | *iii. Inappropriate anti-diuresis* | Lung (small cell Ca), prostate, intracranial tumour | ADH or atrial natriuretic factor |
| | *iv. Hypoglycaemia* | Pancreas (islet cell tumour), mesothelioma, fibrosarcoma | Insulin or insulin-like substance |
| | *v. Carcinoid syndrome* | Bronchial carcinoid tumour, carcinoma pancreas, stomach | Serotonin, bradykinin |
| | *vi. Polycythaemia* | Kidney, liver, cerebellar haemangioma | Erythropoietin |
| 2. | NEUROMUSCULAR SYNDROMES | | |
| | *i. Myasthenia gravis* | Thymoma | Immunologic |
| | *ii. Neuromuscular disorders* | Lung (small cell Ca), breast | Immunologic |



| | | |
|---|---|---|
| 3. OSSEOUS, JOINT AND SOFT TISSUE | | |
| *i. Hypertrophic osteoarthropathy* | Lung | Not known |
| *ii. Clubbing of fingers* | Lung | Not known |
| 4. HAEMATOLOGIC SYNDROMES | | |
| *i. Thrombophlebitis* (Trousseau's phenomenon) | Pancreas, lung, GIT | Hypercoagulability |
| *ii. Non-bacterial thrombotic endocarditis* | Advanced cancers | Hypercoagulability |
| *iii. Disseminated intravascular coagulation (DIC)* | AML, adenocarcinoma | Chronic thrombotic phenomena |
| *iv. Anaemia* | Thymoma | Unknown |
| 5. GASTROINTESTINAL SYNDROMES | | |
| *i. Malabsorption* | Lymphoma of small bowel | Hypoalbuminaemia |
| 6. RENAL SYNDROMES | | |
| *i. Nephrotic syndrome* | Advanced cancers | Renal vein thrombosis, systemic amyloidosis |
| 7. CUTANEOUS SYNDROMES | | |
| *i. Acanthosis nigricans* | Stomach, large bowel | Immunologic |
| *ii. Seborrheic dermatitis* | Bowel | Immunologic |
| *iii. Exfoliative dermatitis* | Lymphoma | Immunologic |
| 8. AMYLOIDOSIS | | |
| *i. Primary* | Multiple myeloma | Immunologic (AL protein) |
| *ii. Secondary* | Kidney, lymphoma, solid tumours | AA protein |

- Most common tumor associated with paraneoplastic syndrome is **small cell carcinoma of lung**

- **Hypercalcemia** is the most comon paraneoplastic syndrome. Most commonly it is caused by **parathyroid hormone related peptide**

- **Cushing's syndrome** is most common endocrinopathy. It is usually due to production of ectopic ACTH by small cell carcinoma lung(most common), carcinoid tumor (neuroendocrine tumor), pancreatic tumor (islet cell tumor), and medullary carcinoma of thyroid.

# POLLS 4

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**Cancer cachexia is due to?**

a) TNF-α
b) IL-5
c) IL-8
d) Phopholipase A2

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# A

**Hypercalcemia is seen in which cancer -**

a) RCC
b) Carcinoma stomach
c) Small cell carcinoma lung
d) Hepatocellular carcinoma

Dr. PRIYA

# A

**In tumor lysis syndrome, all of the following are seen, except:**

(a) Hypernatremia
(b) Hypercalcemia
(c) Hyperkalemia
(d) Hyperphosphatemia

# B

**A 65 years old male diagnosed by biopsy a case of lung carcinoma, with paraneoplastic syndrome and increased calcium. Probable cause is**

(a) Parathyroid hormone
(b) Parathyroid hormone related peptide
(c) Calcitonin
(d) Calcitonin related peptide

Dr. PRIYANK

# B

**Which is associated with polycythemia:**

(a) Gastric carcinoma
(b) Fibrosarcoma
(c) Cerebellar hemangioblastoma
(d) All

Dr. PRIYAN

# c

| | CLINICAL SYNDROME | UNDERLYING CANCER | MECHANISM |
|---|---|---|---|
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# DIAGNOSIS OF CANCER

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# DIAGNOSIS OF CANCER

1. Histological method
2. Cytological method
3. Histochemistry and Cytochemistry
4. Immunohistochemistry (IHC)
5. Electron microscopy
6. Tumour markers
7. Others

# 1. HISTOLOGICAL METHODS

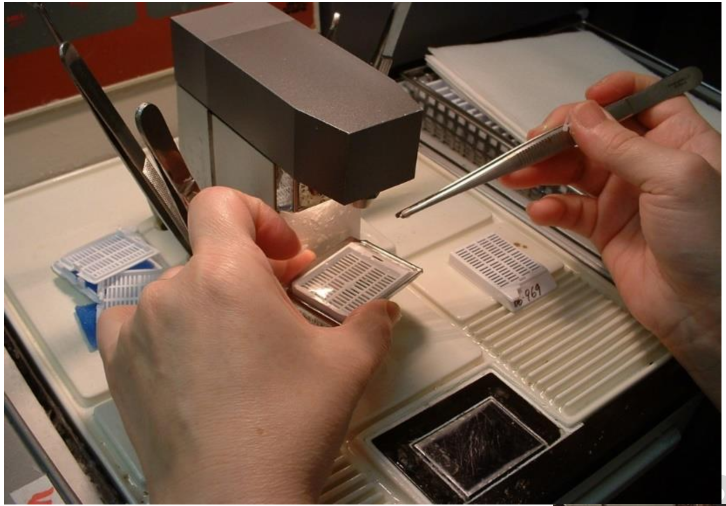
- The tissue must be fixed in 10% formalin for light microscopic examination

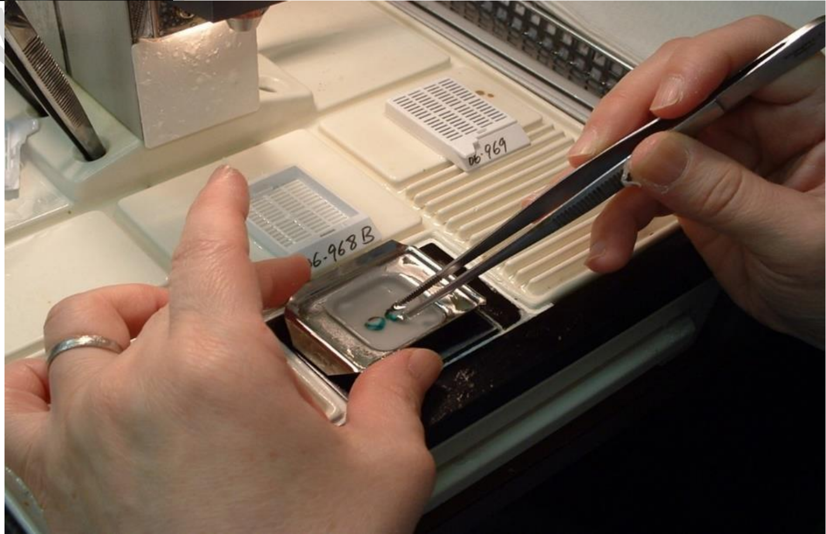
✓ Paraffin embedded technique

✓ Frozen section

# i) Paraffin-embedding technique

- 10% formalin fixed tissue
- Processed through a tissue processor having an overnight cycle
- Embedded in molten paraffin wax for making tissue blocks.
- These blocks are fine-sectioning into 3-4 µm sections using rotary microtome
- Stained with haematoxylin and eosin (H & E)
- Examined microscopically.

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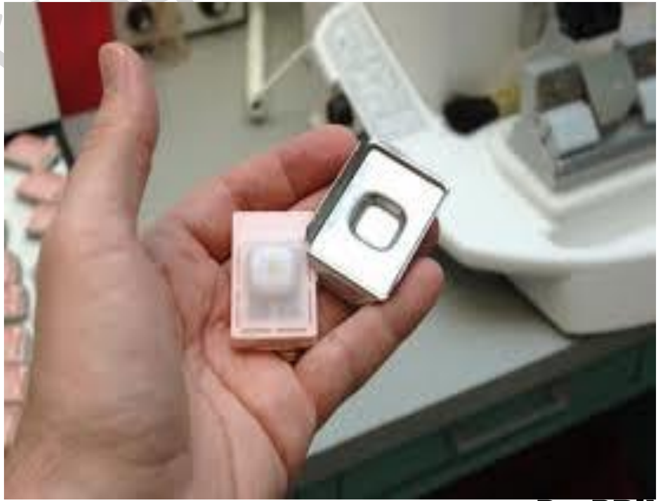

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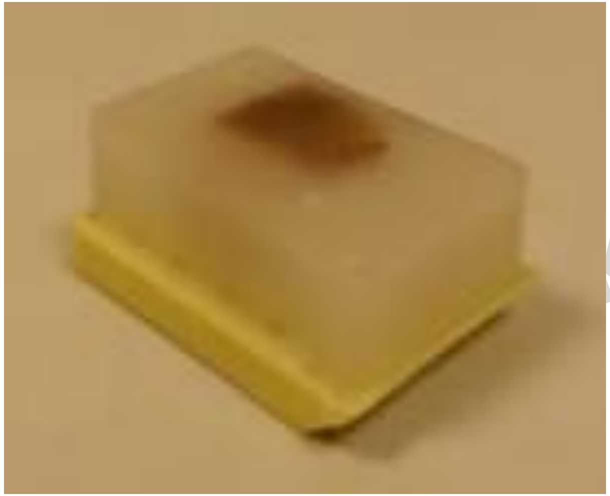
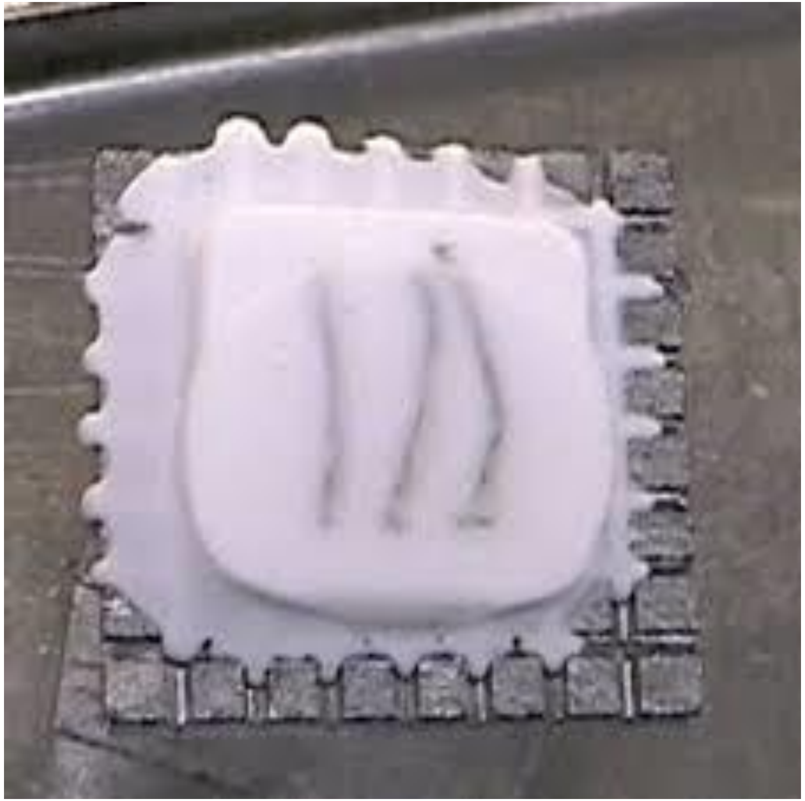


# ii) Frozen section

- **Procedure is generally carried out when the patient is undergoing surgery**
- Unfixed tissue is used
- Tissue is embedded in **ice instead of paraffin wax** , so called as frozen section
- Cryostat machine is used
- Tissue is Sectioned
- Rapid H & E or toluidine blue staining.
- Frozen section is a rapid intraoperative diagnostic procedure for tissues before proceeding to a major radical surgery



Dr

# DIAGNOSIS OF CANCER

1. Histological method
2. Cytological method
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4. Immunohistochemistry (IHC)
5. Electron microscopy
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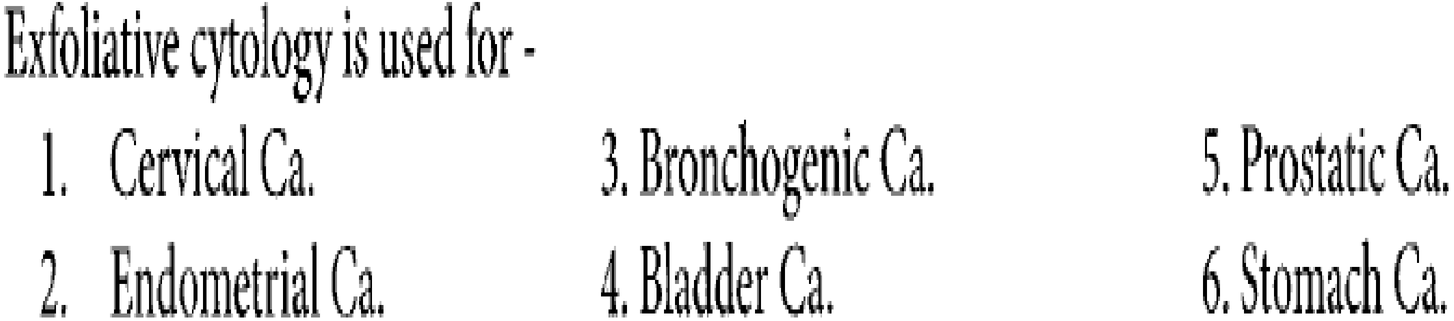
7. Others

# 2. CYTOLOGICAL METHODS

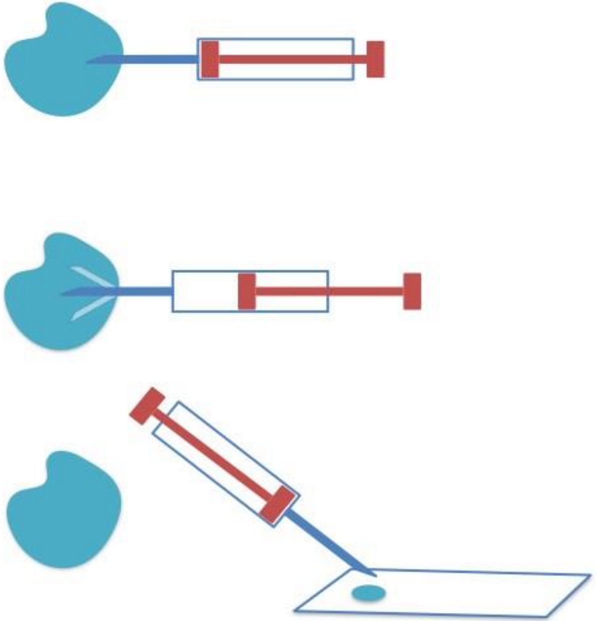
- 2 types →
- study of cells shed off into body cavities (**exfoliative cytology**)
- study of cells by putting a fine needle into the lesion (**fine needle aspiration cytology FNAC**).



Exfoliative cytology is used for -

1. Cervical Ca.
2. Endometrial Ca.
3. Bronchogenic Ca.
4. Bladder Ca.
5. Prostatic Ca.
6. Stomach Ca.

# FNAC



The lesion is pierced with a thin (gauge 21-25) needle

The plunger is withdrawn. Without exiting the lesion and without releasing the plunger the needle in moved in an out in different directions

The needle is withdrawn and the material aspirated smeared on to a slide, stained and examined

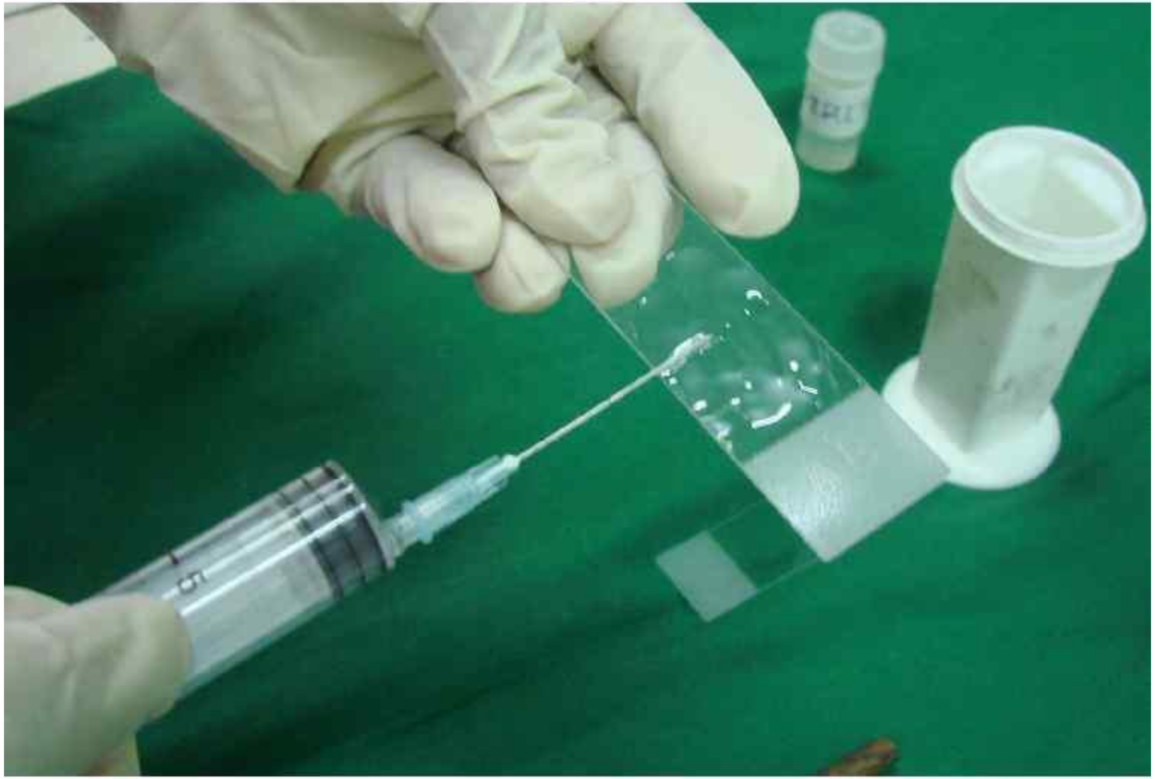
From thecancertextbook.com

**☐ Fine Needle Aspiration Cytology (FNAC)**

- e.g FNA of breast, thyroid, LN, Mass.

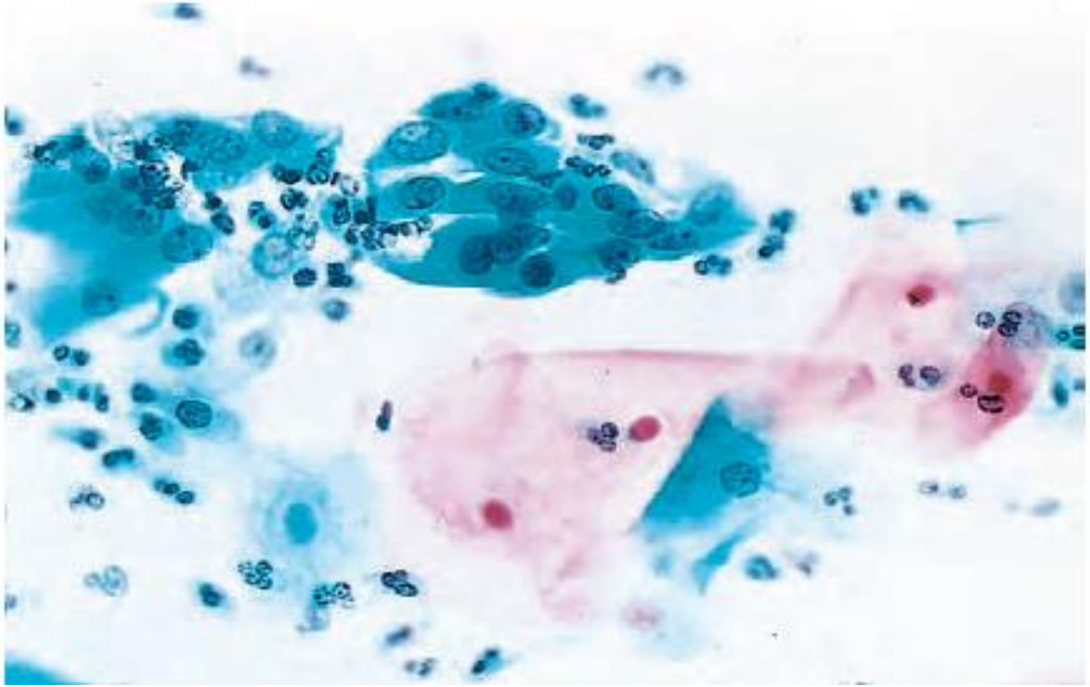
Incision site
Biopsy needle
Sample tissue
Area of concern

# Fine-needle aspiration cytology (FNAC) Test



- Cell morphology and nuclear features is well seen
- Cell architecture is not seen

- Less invasive and more cost effective than histology



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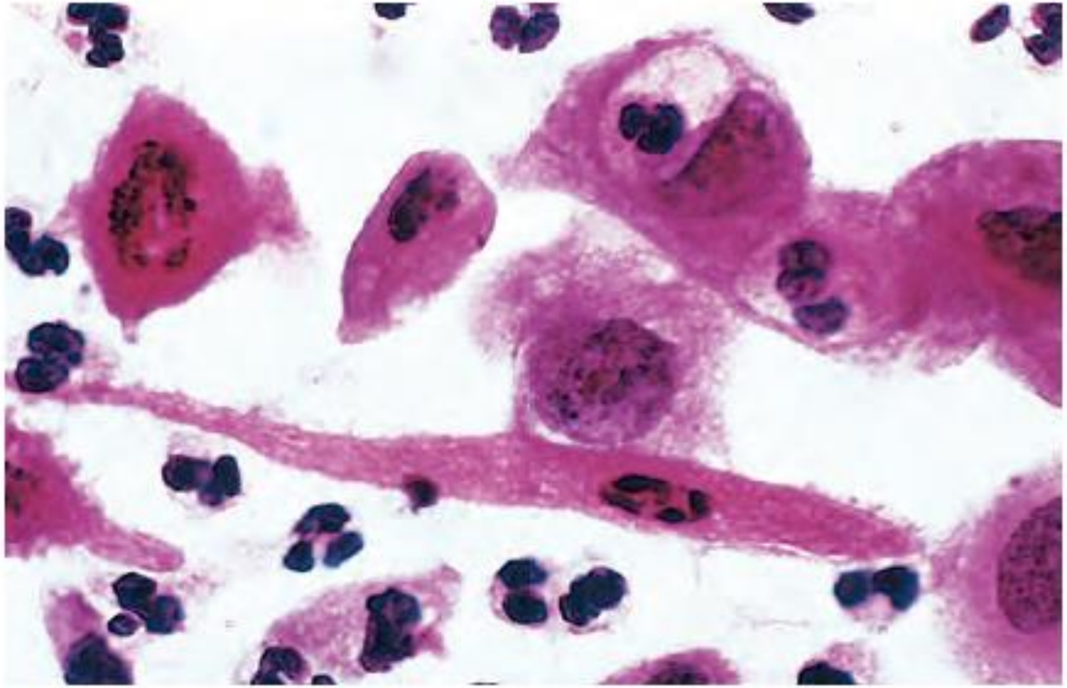
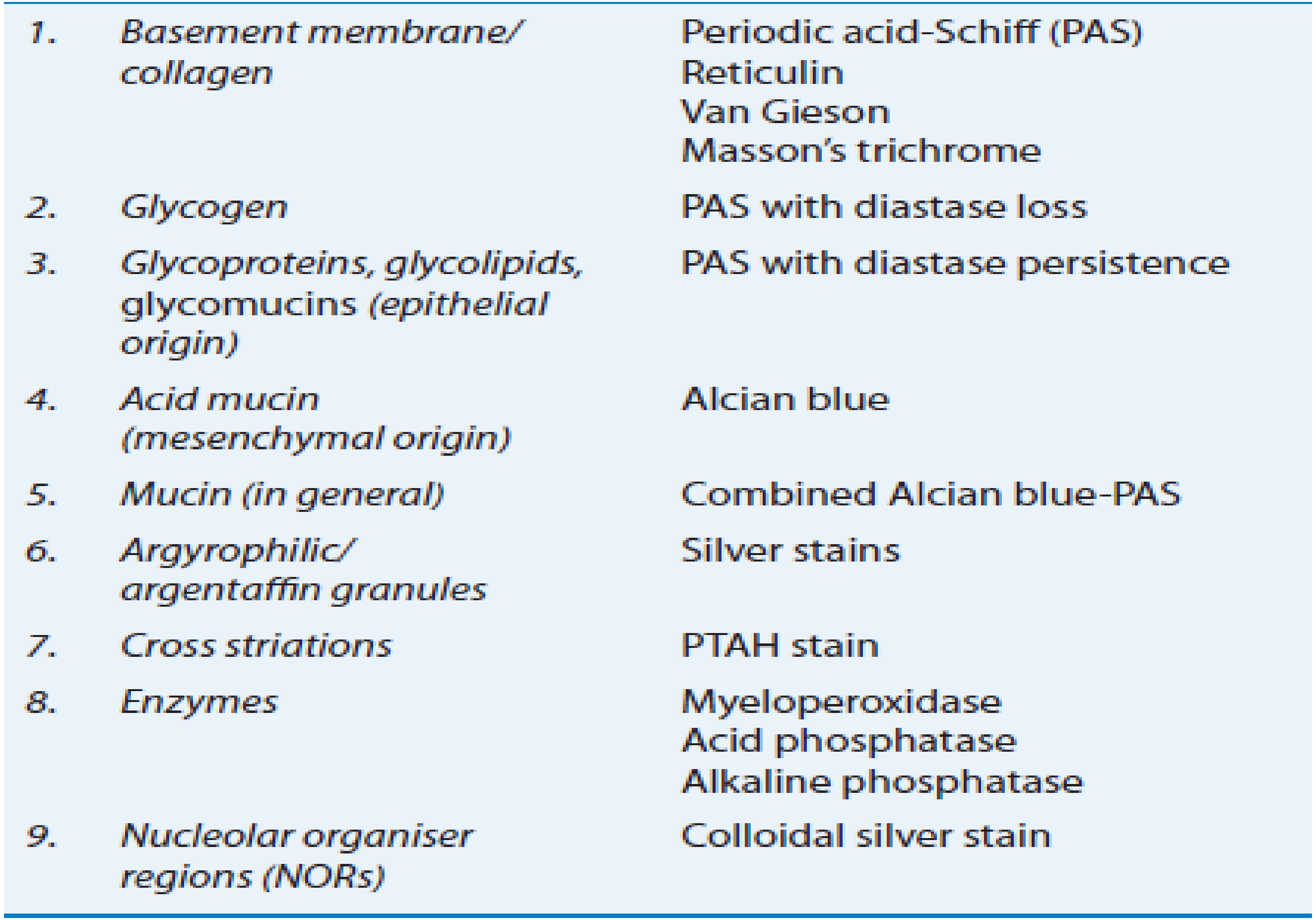


# DIAGNOSIS OF CANCER

1. Histological method
2. Cytological method
3. Histochemistry and Cytochemistry
4. Immunohistochemistry (IHC)
5. Electron microscopy
6. Tumour markers
7. Others

# 3. HISTOCHEMISTRY AND CYTOCHEMISTRY

follow us



| | | |
|---|---|---|
| 1. | *Basement membrane/ collagen* | Periodic acid-Schiff (PAS)<br>Reticulin<br>Van Gieson<br>Masson's trichrome |
| 2. | *Glycogen* | PAS with diastase loss |
| 3. | *Glycoproteins, glycolipids,* glycomucins *(epithelial origin)* | PAS with diastase persistence |
| 4. | *Acid mucin (mesenchymal origin)* | Alcian blue |
| 5. | *Mucin (in general)* | Combined Alcian blue-PAS |
| 6. | *Argyrophilic/ argentaffin granules* | Silver stains |
| 7. | *Cross striations* | PTAH stain |
| 8. | *Enzymes* | Myeloperoxidase<br>Acid phosphatase<br>Alkaline phosphatase |
| 9. | *Nucleolar organiser regions (NORs)* | Colloidal silver stain |

# DIAGNOSIS OF CANCER

1. Histological method
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5. Electron microscopy
6. Tumour markers
7. Others

# 4. IMMUNOHISTOCHEMISTRY (IHC)

- Immunohistochemistry is a method of analyzing and identifying cell types based on binding of antibodies to specific components of the cell.

- Antibody, which is specific for an antigen of a particular tissue, is labled with a probe (coloured marker) and is run on the tissue specimen obtained from a biopsy.

- If the tissue has that particular antigen, then antibody will get attached to the tissue and the labled antibody can be seen under a microscope.

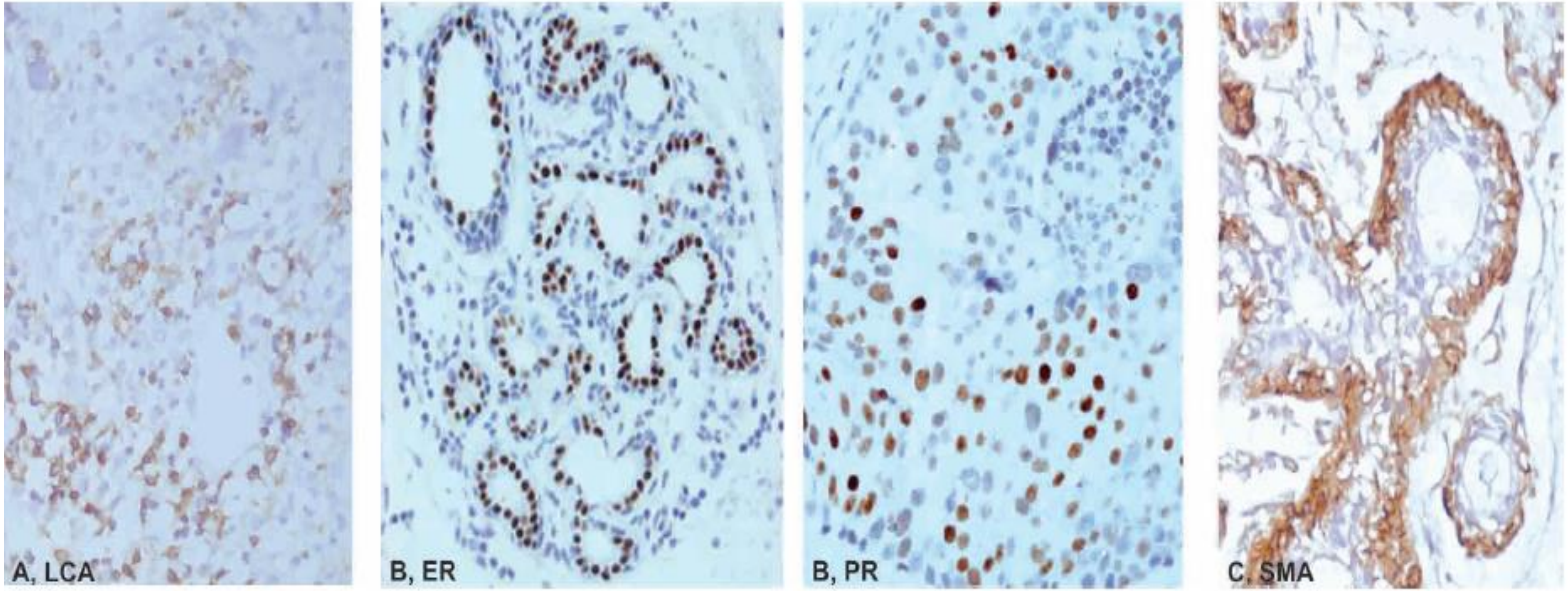
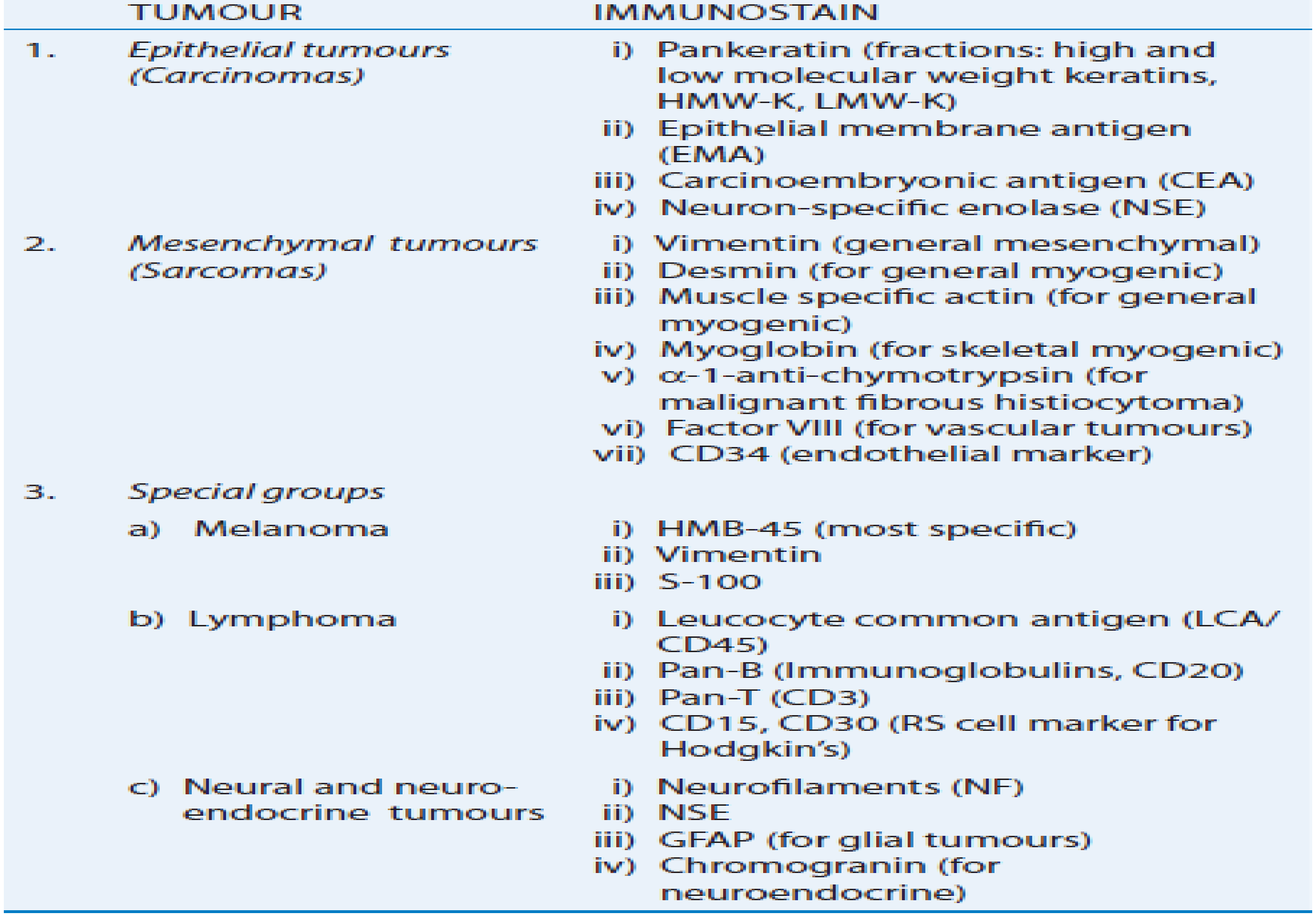


**Figure 7.32** Examples of IHC staining at different sites in the tumour cells. A, Membranous staining for leucocyte common antigen (LCA) or CD45 in lymphomas. B, Cytoplasmic staining for smooth muscle actin (SMA) in myoepithelium on breast acinus. C, Nuclear staining for breast ER-PR receptor studies in breast cancer.

# IHC



|  | TUMOUR | IMMUNOSTAIN |
|---|---|---|
| 1. | *Epithelial tumours (Carcinomas)* | i) Pankeratin (fractions: high and low molecular weight keratins, HMW-K, LMW-K)<br>ii) Epithelial membrane antigen (EMA)<br>iii) Carcinoembryonic antigen (CEA)<br>iv) Neuron-specific enolase (NSE) |
| 2. | *Mesenchymal tumours (Sarcomas)* | i) Vimentin (general mesenchymal)<br>ii) Desmin (for general myogenic)<br>iii) Muscle specific actin (for general myogenic)<br>iv) Myoglobin (for skeletal myogenic)<br>v) α-1-anti-chymotrypsin (for malignant fibrous histiocytoma)<br>vi) Factor VIII (for vascular tumours)<br>vii) CD34 (endothelial marker) |
| 3. | *Special groups* |  |
|  | a) Melanoma | i) HMB-45 (most specific)<br>ii) Vimentin<br>iii) S-100 |
|  | b) Lymphoma | i) Leucocyte common antigen (LCA/CD45)<br>ii) Pan-B (Immunoglobulins, CD20)<br>iii) Pan-T (CD3)<br>iv) CD15, CD30 (RS cell marker for Hodgkin's) |
|  | c) Neural and neuro-endocrine tumours | i) Neurofilaments (NF)<br>ii) NSE<br>iii) GFAP (for glial tumours)<br>iv) Chromogranin (for neuroendocrine) |

# DIAGNOSIS OF CANCER

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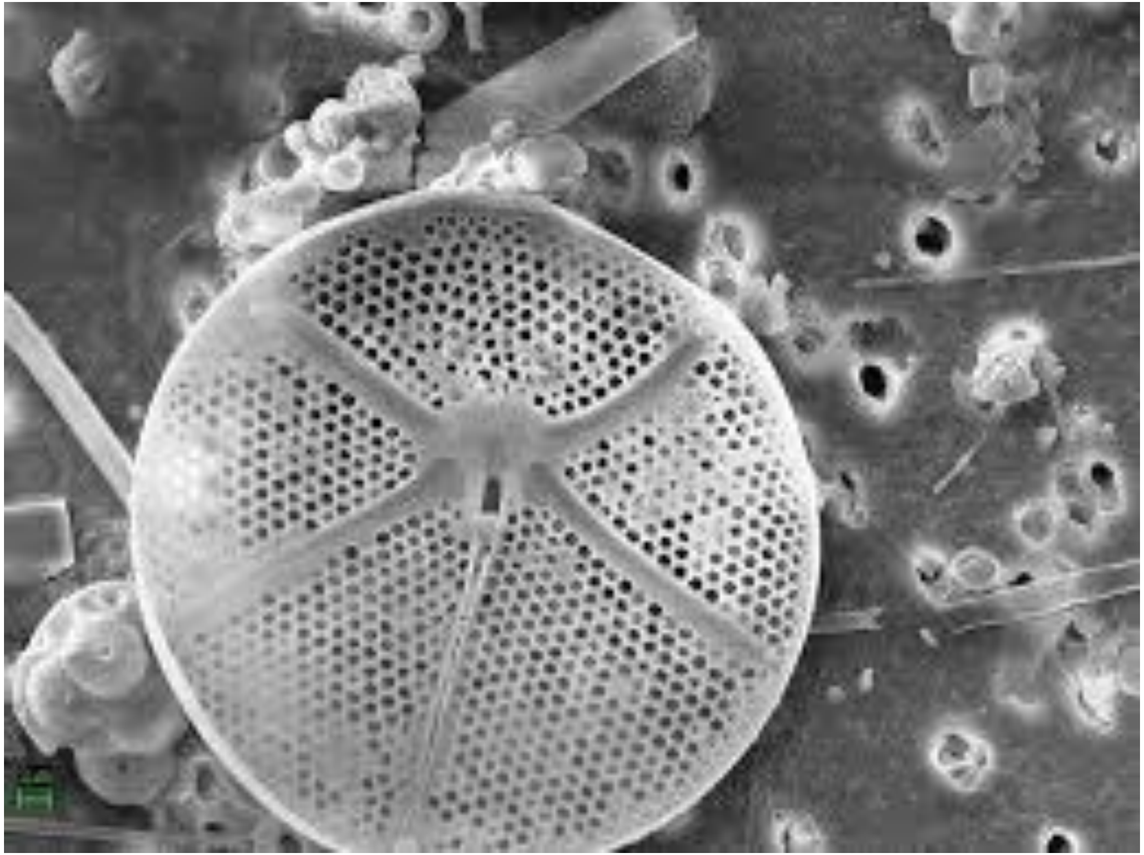
# 5. ELECTRON MICROSCOPY

- Ultrastructural examination of tumour cells

- A few general features

i) Cell junctions, their presence and type.
ii) Cell surface, e.g. presence of microvilli.
iii) Cell shape and cytoplasmic extensions.
iv) Shape of the nucleus and features of nuclear membrane.
v) Nucleoli, their size and density.
vi) Cytoplasmic organelles—their number is generally reduced.
vii) Dense bodies in the cytoplasm



# DIAGNOSIS OF CANCER

1. Histological method
2. Cytological method
3. Histochemistry and Cytochemistry
4. Immunohistochemistry (IHC)
5. Electron microscopy
6. Tumour markers
7. Others

# 6. TUMOUR MARKERS (BIOCHEMICAL ASSAYS)

- Some tumor produce or elicite the production of **markers that can be measured in the serum or urine or other body fluids.**
- Tumor markers are **biochemical indicators of the presence of a tumor.**

- Markers may be cell surface antigen, enzymes, hormones, tumor associated protein, or oncofetal antigens.

- Many of these products are produced by normal body cells too
- thus the biochemical estimation of the product in blood reflects total substance and not by the tumour cells alone.
- So lack sensitivity as well as specificity
- Use as an adjunct to the pathologic diagnosis and for prognostic and therapeutic purposes

# The ideal tumor marker should be

- ✓ Present only in tumor cells
- ✓ Specific for the organ and type of tumor
- ✓ Assessable in the sera of all patients with the same type of tumor
- ✓ Assessable in the serum at the very beginning of tumor development
- ✓ Concentrations in the serum should correlate with the tumor burden

# Clinical applications

- Screening in general population
- Diagnosis in symptomatic patients
- Estimating tumor volume
- Prognostic indicator of disease progression
- Monitoring responses to therapy
- Detecting the recurrence of cancer

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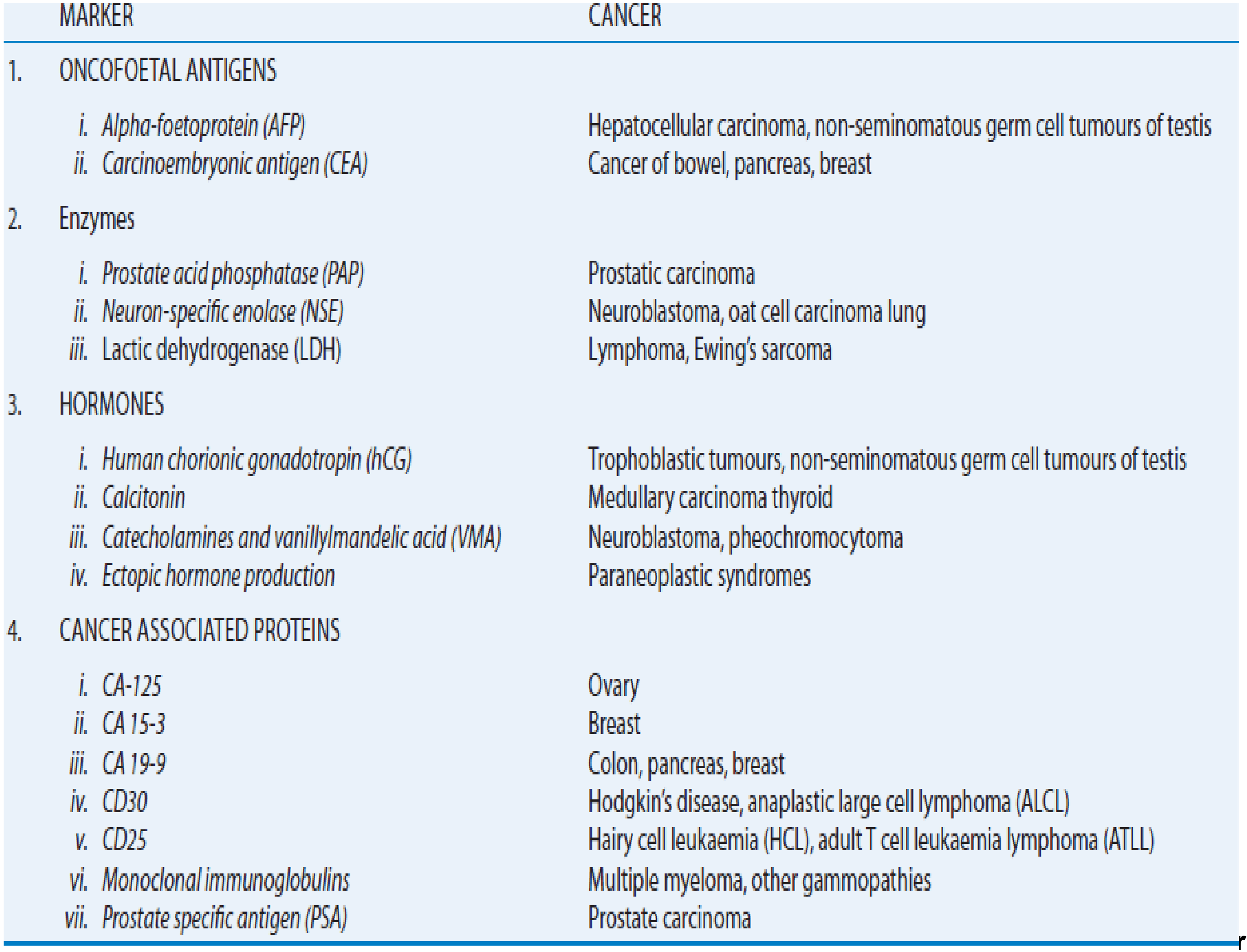

| | MARKER | CANCER |
|---|---|---|
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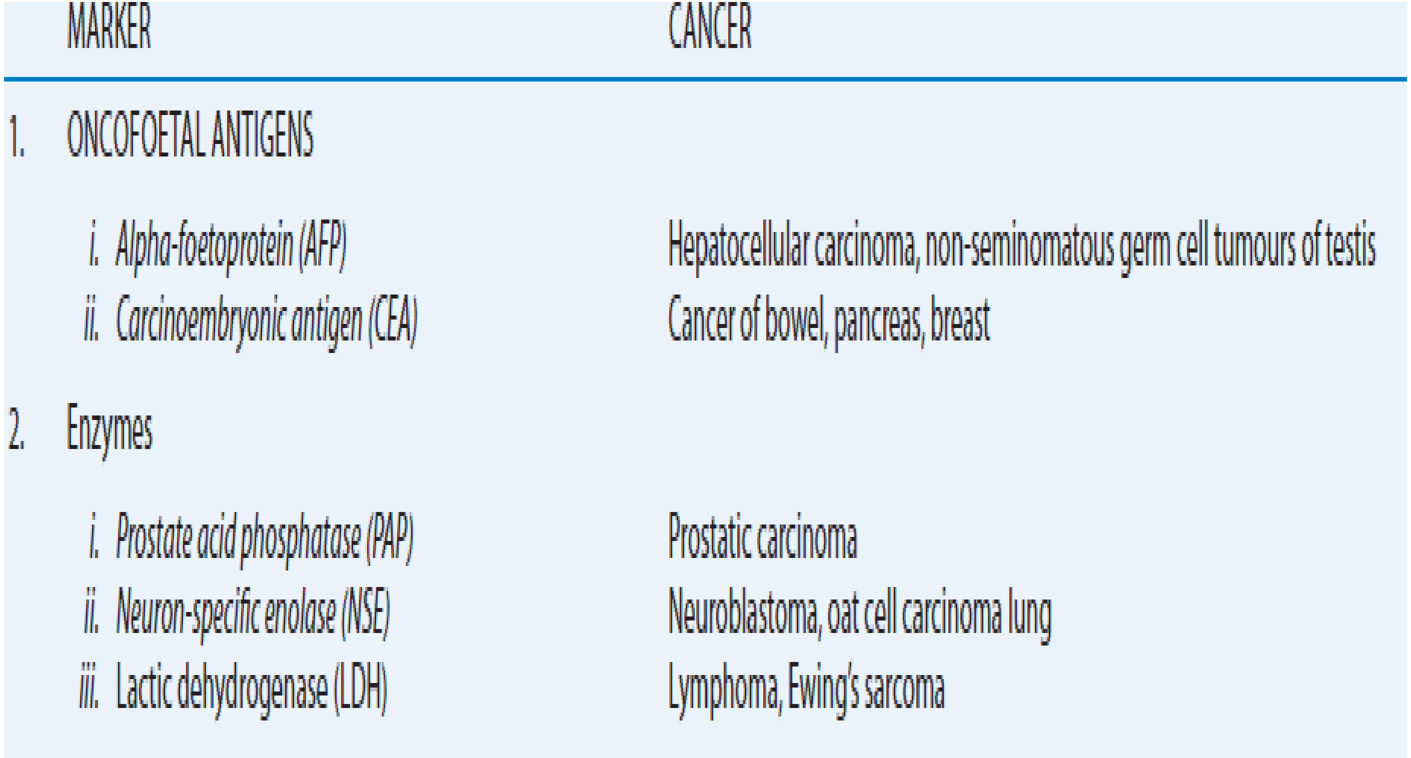
| | *i. Alpha-foetoprotein (AFP)* | Hepatocellular carcinoma, non-seminomatous germ cell tumours of testis |
| | *ii. Carcinoembryonic antigen (CEA)* | Cancer of bowel, pancreas, breast |
| 2. | Enzymes | |
| | *i. Prostate acid phosphatase (PAP)* | Prostatic carcinoma |
| | *ii. Neuron-specific enolase (NSE)* | Neuroblastoma, oat cell carcinoma lung |
| | *iii.* Lactic dehydrogenase (LDH) | Lymphoma, Ewing's sarcoma |
| 3. | HORMONES | |
| | *i. Human chorionic gonadotropin (hCG)* | Trophoblastic tumours, non-seminomatous germ cell tumours of testis |
| | *ii. Calcitonin* | Medullary carcinoma thyroid |
| | *iii. Catecholamines and vanillylmandelic acid (VMA)* | Neuroblastoma, pheochromocytoma |
| | *iv. Ectopic hormone production* | Paraneoplastic syndromes |
| 4. | CANCER ASSOCIATED PROTEINS | |
| | *i. CA-125* | Ovary |
| | *ii. CA 15-3* | Breast |
| | *iii. CA 19-9* | Colon, pancreas, breast |
| | *iv. CD30* | Hodgkin's disease, anaplastic large cell lymphoma (ALCL) |
| | *v. CD25* | Hairy cell leukaemia (HCL), adult T cell leukaemia lymphoma (ATLL) |
| | *vi. Monoclonal immunoglobulins* | Multiple myeloma, other gammopathies |
| | *vii. Prostate specific antigen (PSA)* | Prostate carcinoma |



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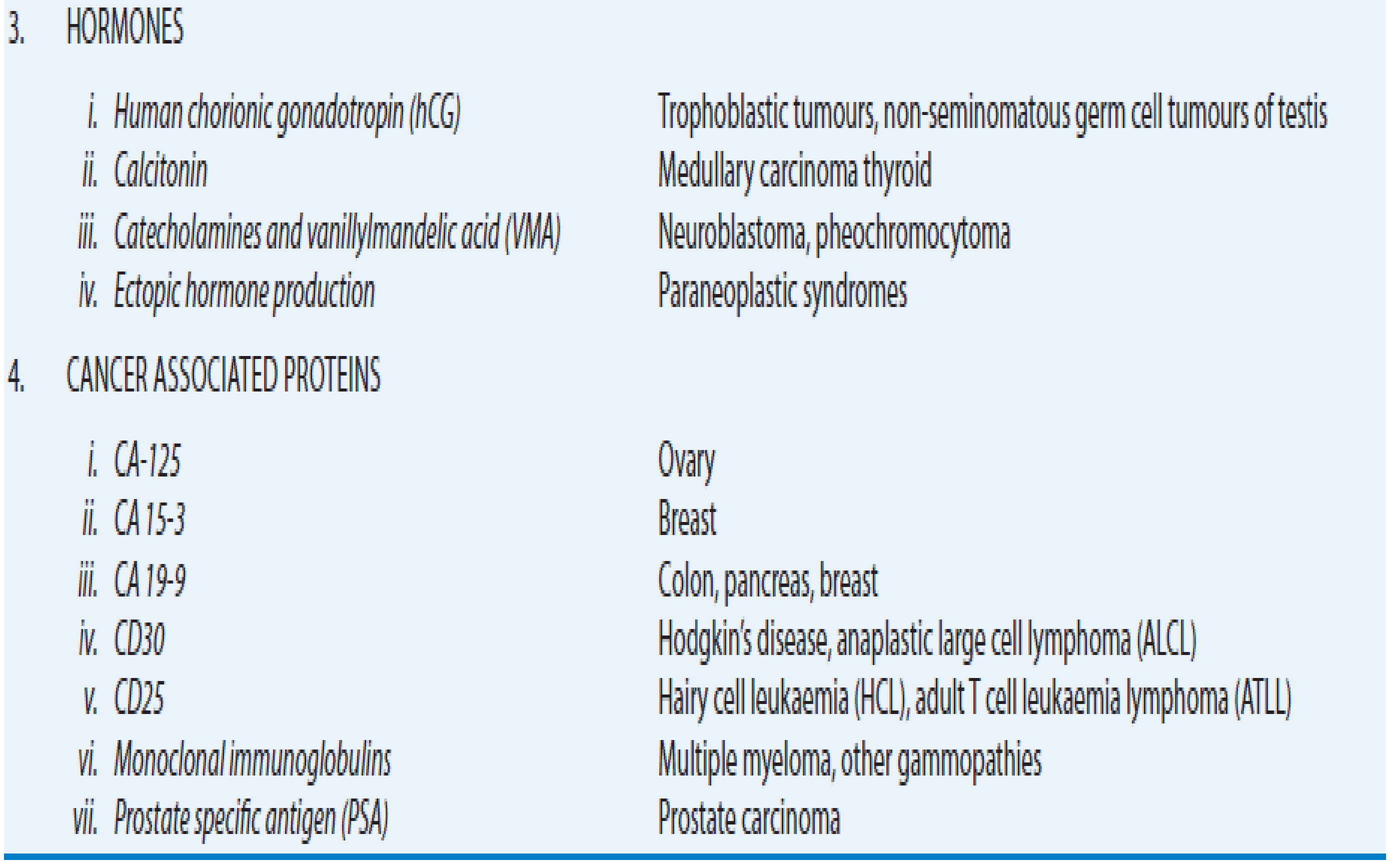

| | |
|---|---|
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| *i. Human chorionic gonadotropin (hCG)* | Trophoblastic tumours, non-seminomatous germ cell tumours of testis |
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## Tumor Associated Proteins

| | |
|---|---|
| *Prostatic-specific antigen*$^{([illegible])}$ | *Prostate cancer*$^{([illegible])}$ |
| Monoclonal immunoglobulin | Myeloma |
| CA - 125 | Ovarian cancer, some lymphomas |
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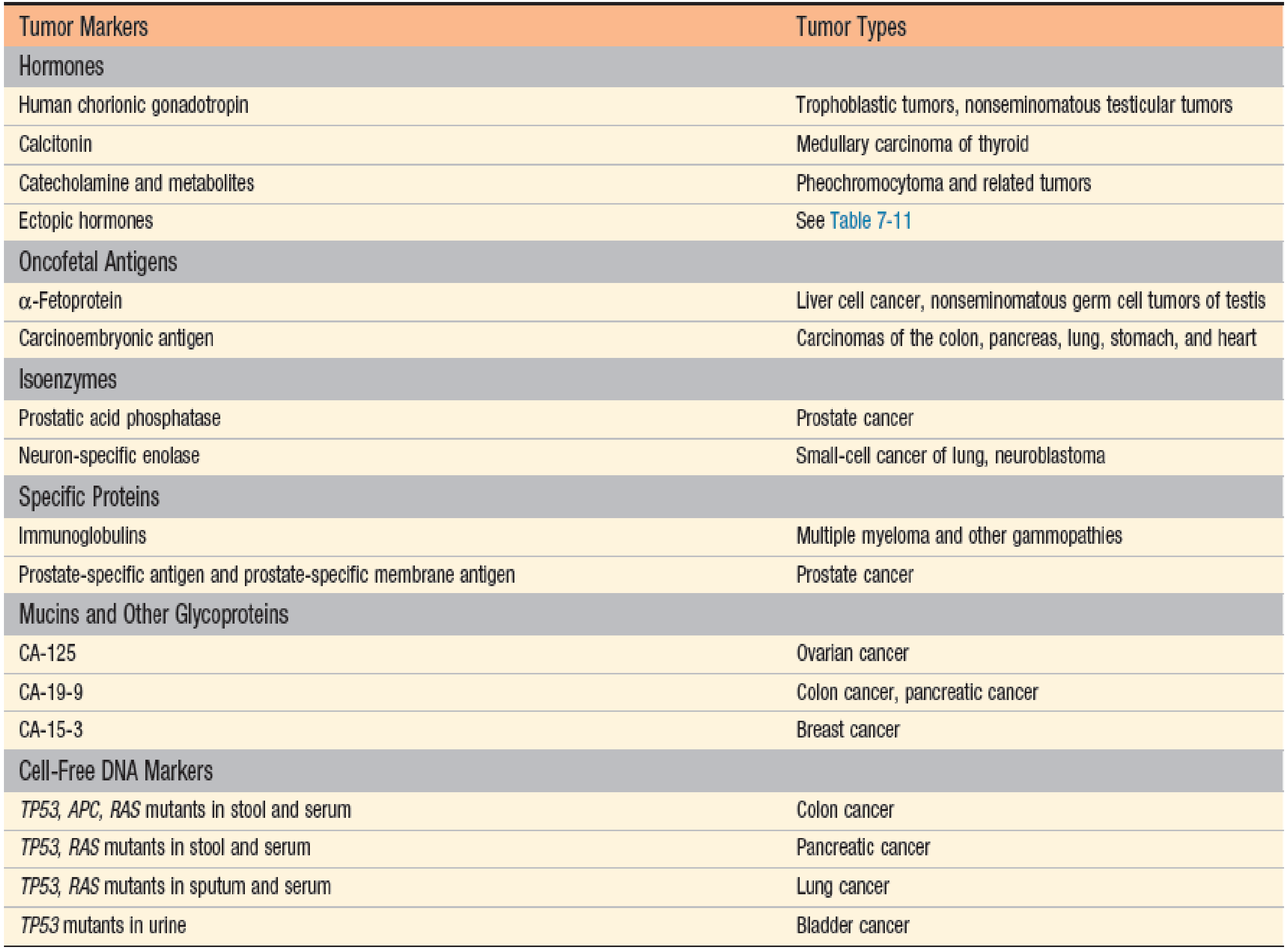
| CA 27.29 & CA 15-3 | Breast cancer |
| CD 30 | Hodgkin's disease, anaplastic large cell lymphoma |
| CD 25 | Hairy cell leukemia, adult T cell leukemia / lymphoma |
| ***CD-34*** | ***Alveolar soft part sarcoma***$^{(NEET)}$ |
| $\beta_2$ - ***Microglobulin***$^{(AIIMS\ 04)}$ | Multiple myeloma |
| ***S-100, HMB-45***$^{(AI\ 08)}$***, TA-90*** | Malignant melanoma |
| NMP-22 | Urinary bladder Ca |
| ***CD-99***$^{(AIIMS\ 08)}$ | ***Ewing's sarcoma***$^{(AIIMS\ 08)}$ |

**New Molecular markers**



| Tumor Markers | Tumor Types |
|---|---|
| **Hormones** | |
| Human chorionic gonadotropin | Trophoblastic tumors, nonseminomatous testicular tumors |
| Calcitonin | Medullary carcinoma of thyroid |
| Catecholamine and metabolites | Pheochromocytoma and related tumors |
| Ectopic hormones | See Table 7-11 |
| **Oncofetal Antigens** | |
| α-Fetoprotein | Liver cell cancer, nonseminomatous germ cell tumors of testis |
| Carcinoembryonic antigen | Carcinomas of the colon, pancreas, lung, stomach, and heart |
| **Isoenzymes** | |
| Prostatic acid phosphatase | Prostate cancer |
| Neuron-specific enolase | Small-cell cancer of lung, neuroblastoma |
| **Specific Proteins** | |
| Immunoglobulins | Multiple myeloma and other gammopathies |
| Prostate-specific antigen and prostate-specific membrane antigen | Prostate cancer |
| **Mucins and Other Glycoproteins** | |
| CA-125 | Ovarian cancer |
| CA-19-9 | Colon cancer, pancreatic cancer |
| CA-15-3 | Breast cancer |
| **Cell-Free DNA Markers** | |
| *TP53, APC, RAS* mutants in stool and serum | Colon cancer |
| *TP53, RAS* mutants in stool and serum | Pancreatic cancer |
| *TP53, RAS* mutants in sputum and serum | Lung cancer |
| *TP53* mutants in urine | Bladder cancer |

**Dr. PRIYANKA SACHDEV**

# α-fetoprotein

- Glycoprotein
- Synthesized by fetal yolk sac and liver
- It is structurally and genetically related to albumin
- Normal value → < 10 μg/L

# Clinical applications

1. Specific and ideal marker for **hepatocellular carcinoma, and non-seminomatous germ cell tumours of the testis.**

2. Certain non-neoplastic conditions e.g. in **hepatitis, cirrhosis, toxic liver injury and pregnancy.**

- Serum levels correlates with the size of tumors
- Useful in screening in high risk areas
- Useful in determining prognosis and in the monitoring of therapy for hepatocellular carcinoma
- Level is a prognostic indicator of survival
- Elevated levels >10 µg/L as well as serum bilirubin >2mg/dL are associated with shorter survival time

# Carcinoembryonic Antigen (CEA)

- glycoprotein
- synthesized normally in fetal life by yolk sac, fetal liver and fetal GIT.

Normal value

1. non smokers 3 µg/L
2. smokers 5 µg/L

# Clinical applications

1. Most useful marker in the **colorectal carcinoma, in cancers of the gastrointestinal tract, pancreas and breast.**

2. certain non-neoplastic conditions e.g. **in ulcerative colitis, Crohn’s disease, hepatitis and chronic bronchitis.**

- CEA levels correlates with the stage of the disease
  - 28% of Duke stage A
  - 45% of Duke stage B

- Pretreatment levels are prognostic of the development of metastasis

- Successful therapy: levels decline
- Remission : levels stable
- Rising levels: indicates recurrence
- Lead time : level rise to clinical recurrence is 5month

- CEA lacks sensitivity as well as specificity, hence cannot be used to confirm the diagnosis

# Human chorionic gonadotropin (HCG)

- It is a placental hormone synthesized by **syncytiotrophoblasts.**

- It is glycoprotein with two subunits (dimer):

1. α-subunit
2. β-subunit.

- **But only the β subunit of HCG is typically measured as a tumour marker** because of specificity of the β subunit.
- The β subunit of HCG has unique sequences that are not shared with other human glycoprotein hormones.
- **α- HCG is not used as tumour marker because α unit of the FSH, LH and TSH are identical**. So there can be cross reactivity between a subunits of these hormone.

# Clinical applications

- HCG (p-HCG) is raised in gestational trophoblastic disease (hydatidiform moles), gonadal germ cell tumor (embryonal carcinoma, choriocarcinoma), and pregnancy.

# POLLS 5

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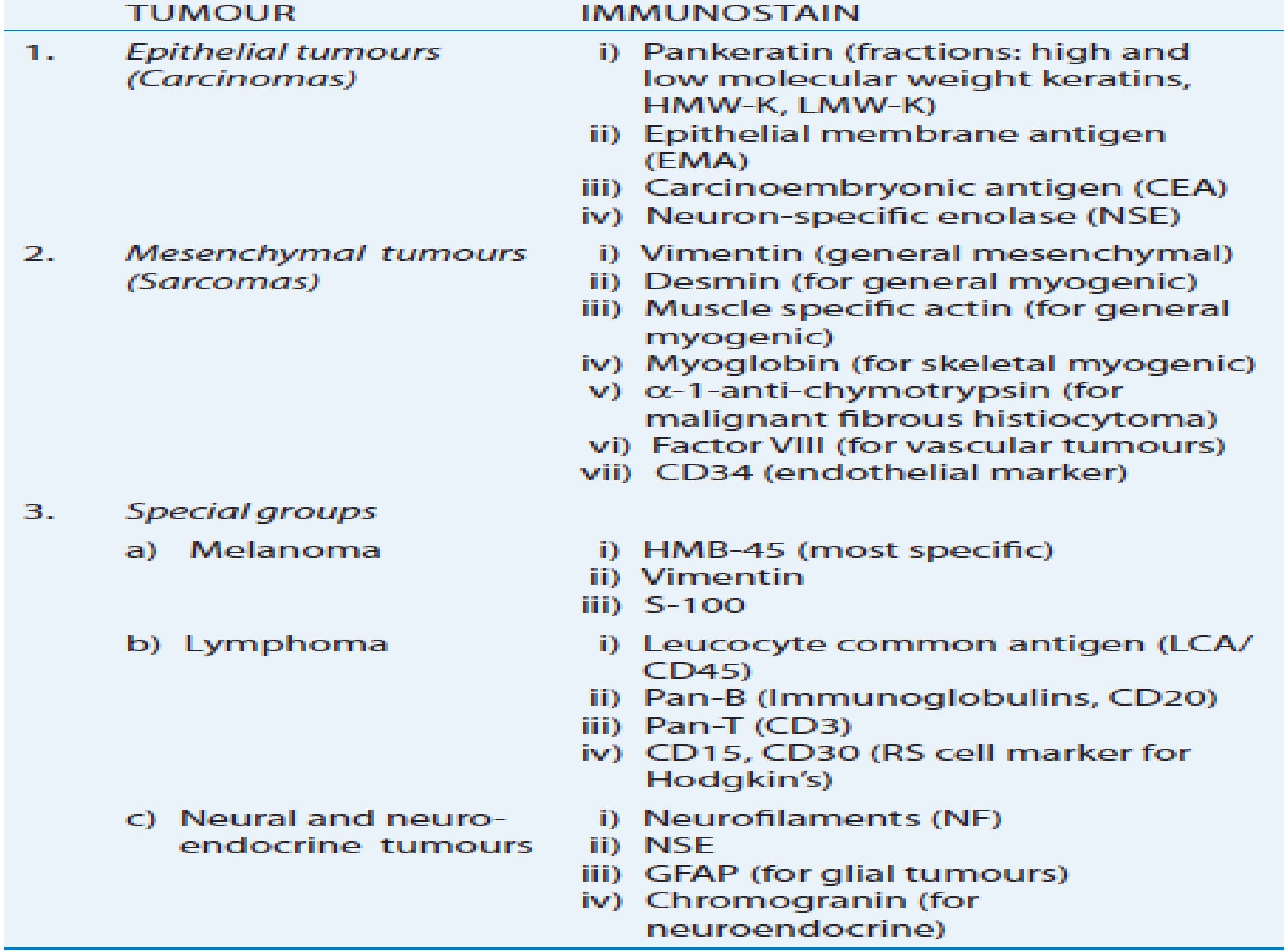
**Melanocytic marker is?**

a) CD99
b) HMB-45
c) NMP-22
d) CA-125

Dr. PRIYANK

# B



| | TUMOUR | IMMUNOSTAIN |
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| 3. | *Special groups* | |
| | a) Melanoma | i) HMB-45 (most specific)<br>ii) Vimentin<br>iii) S-100 |
| | b) Lymphoma | i) Leucocyte common antigen (LCA/CD45)<br>ii) Pan-B (Immunoglobulins, CD20)<br>iii) Pan-T (CD3)<br>iv) CD15, CD30 (RS cell marker for Hodgkin's) |
| | c) Neural and neuro-endocrine tumours | i) Neurofilaments (NF)<br>ii) NSE<br>iii) GFAP (for glial tumours)<br>iv) Chromogranin (for neuroendocrine) |

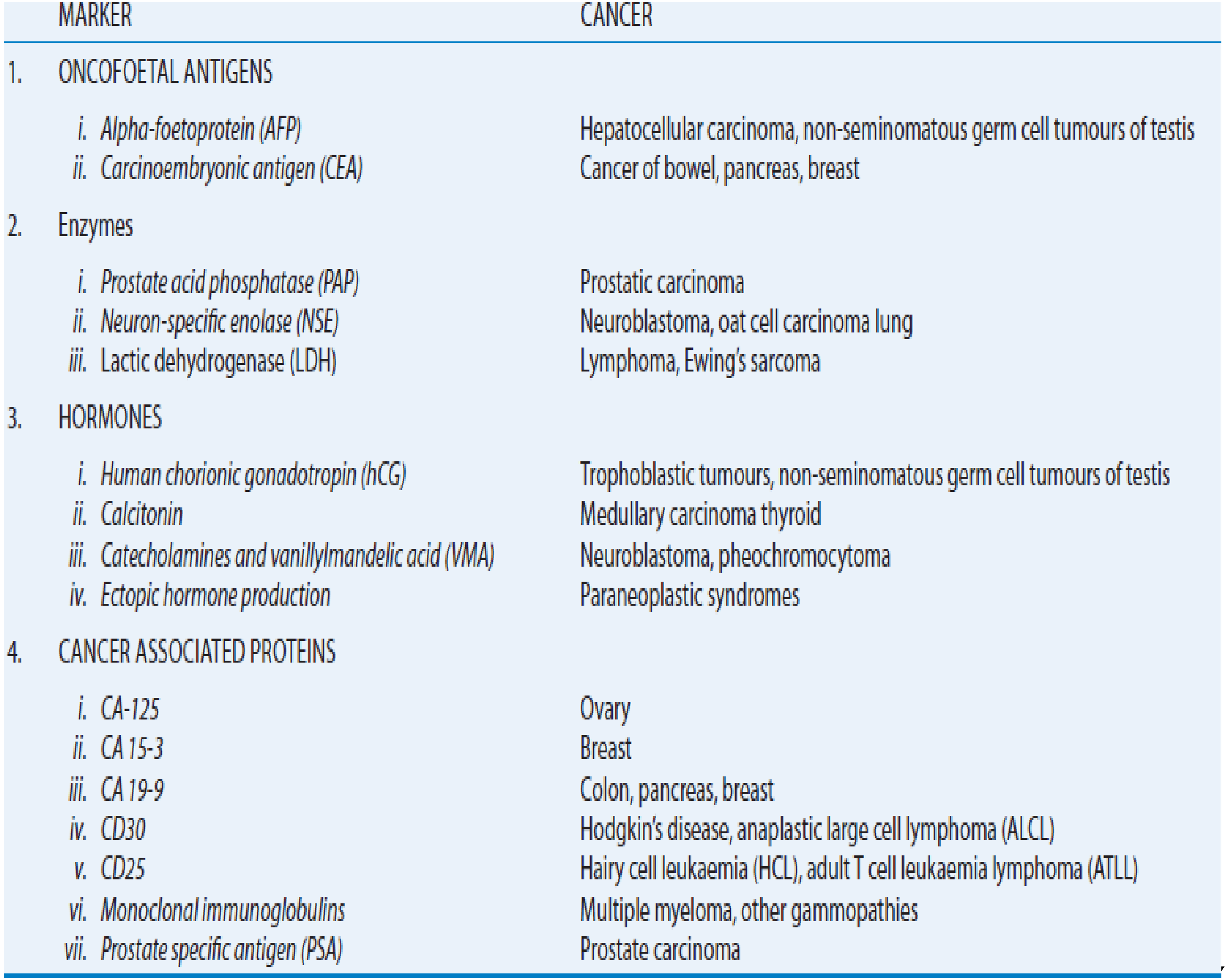
**A SACHDEV**

**Calcitonin is a marker of -**

a) Prostate cancer
b) Medullary carcinoma of thyroid
c) Pheochromocytoma
d) Pancreatic cancer

Dr. PRIYANK

# B



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| | iii. *Catecholamines and vanillylmandelic acid (VMA)* | Neuroblastoma, pheochromocytoma |
| | iv. *Ectopic hormone production* | Paraneoplastic syndromes |
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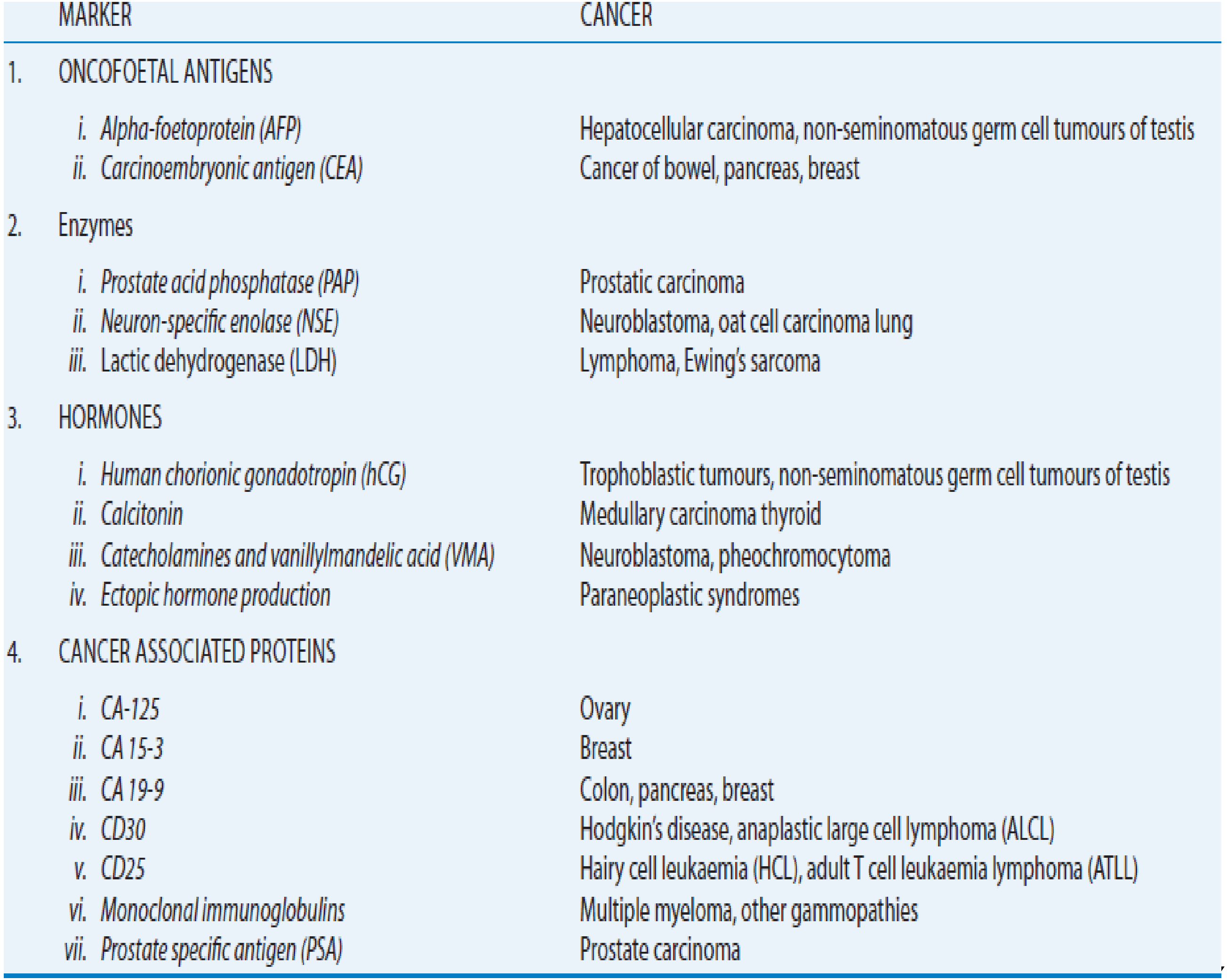
| | v. *CD25* | Hairy cell leukaemia (HCL), adult T cell leukaemia lymphoma (ATLL) |
| | vi. *Monoclonal immunoglobulins* | Multiple myeloma, other gammopathies |
| | vii. *Prostate specific antigen (PSA)* | Prostate carcinoma |

**Which one of the following is not used as a tumor marker in testicular tumours ?**

a) AFP
b) LDH
c) HCG
d) CEA

Dr. PRIYA

# D



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| 2. | Enzymes | |
| | i. *Prostate acid phosphatase (PAP)* | Prostatic carcinoma |
| | ii. *Neuron-specific enolase (NSE)* | Neuroblastoma, oat cell carcinoma lung |
| | iii. Lactic dehydrogenase (LDH) | Lymphoma, Ewing's sarcoma |
| 3. | HORMONES | |
| | i. *Human chorionic gonadotropin (hCG)* | Trophoblastic tumours, non-seminomatous germ cell tumours of testis |
| | ii. *Calcitonin* | Medullary carcinoma thyroid |
| | iii. *Catecholamines and vanillylmandelic acid (VMA)* | Neuroblastoma, pheochromocytoma |
| | iv. *Ectopic hormone production* | Paraneoplastic syndromes |
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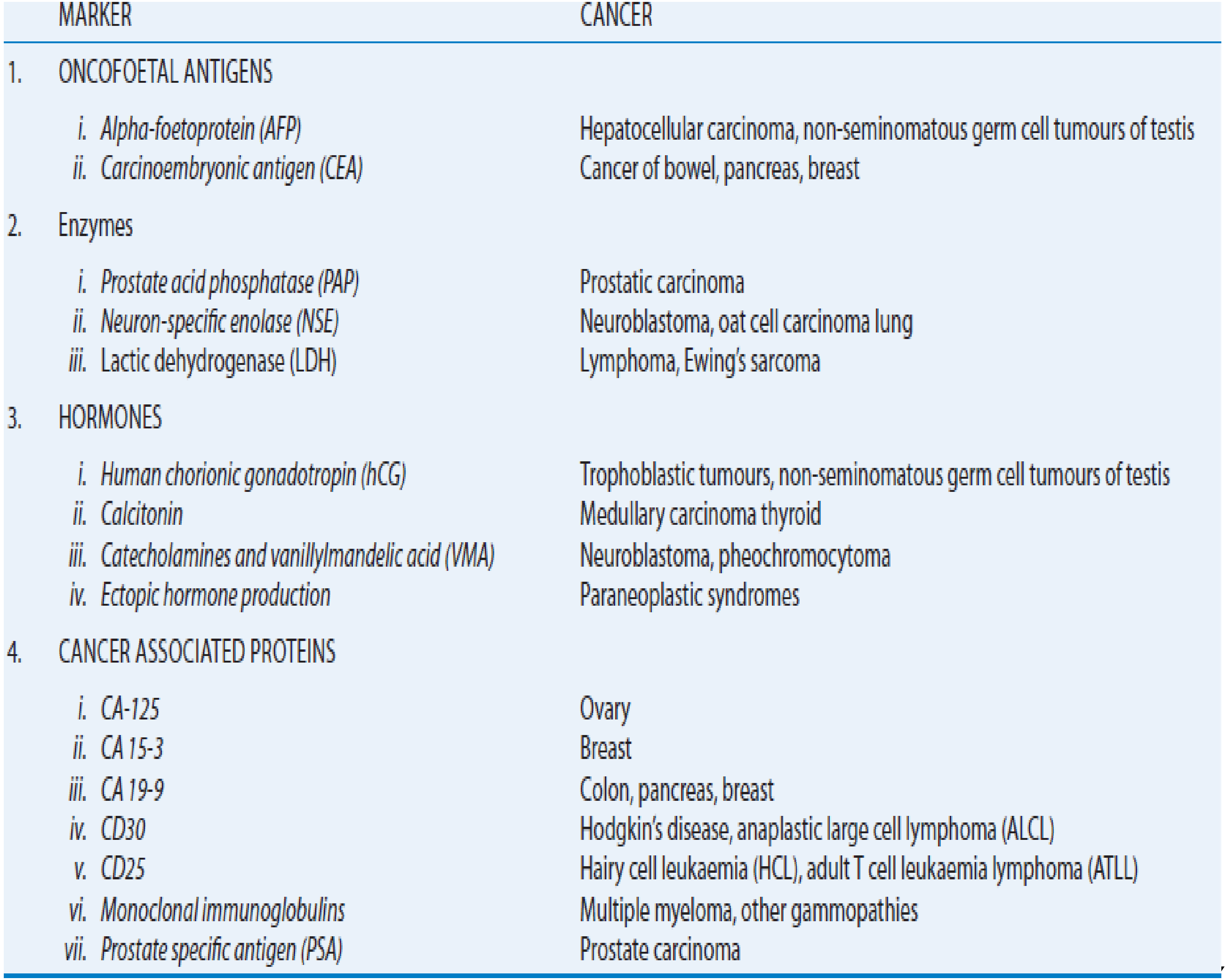
| | v. *CD25* | Hairy cell leukaemia (HCL), adult T cell leukaemia lymphoma (ATLL) |
| | vi. *Monoclonal immunoglobulins* | Multiple myeloma, other gammopathies |
| | vii. *Prostate specific antigen (PSA)* | Prostate carcinoma |

**Serum alpha feto protein level is raised in -**

a) Teratoma
b) Seminoma
c) Endodermal sinus tumor
d) HCG

Dr. PRIYAN

# A



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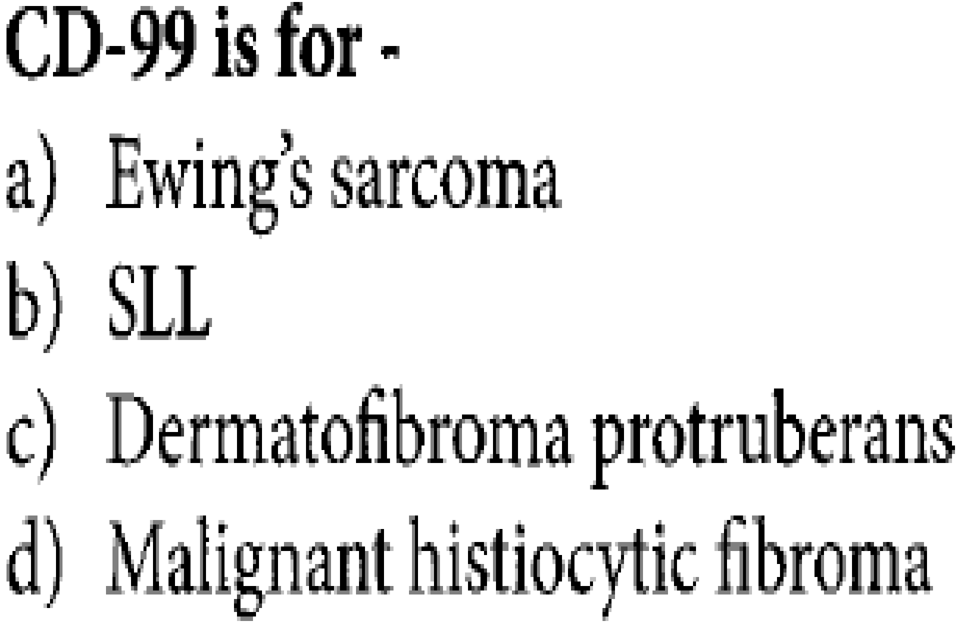
**ANKA SACHDEV**



**CD-99 is for -**

a) Ewing's sarcoma

b) SLL

c) Dermatofibroma protruberans

d) Malignant histiocytic fibroma

# A

**Tumor Associated Proteins**

| | |
|---|---|
| *Prostatic-specific antigen*$^{\text{[illegible]}}$ | • *Prostate cancer*$^{\text{[illegible]}}$ |
| Monoclonal immunoglobulin | • Myeloma |
| CA - 125 | • Ovarian cancer, some lymphomas |
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| $\beta_2$ - ***Microglobulin***$^{(\text{AIIMS 04})}$ | • Multiple myeloma |
| ***S-100, HMB-45***$^{(\text{AI 08})}$***, TA-90*** | • Malignant melanoma |
| NMP-22 | • Urinary bladder Ca |
| ***CD-99***$^{(\text{AIIMS 08})}$ | • ***Ewing's sarcoma***$^{(\text{AIIMS 08})}$ |

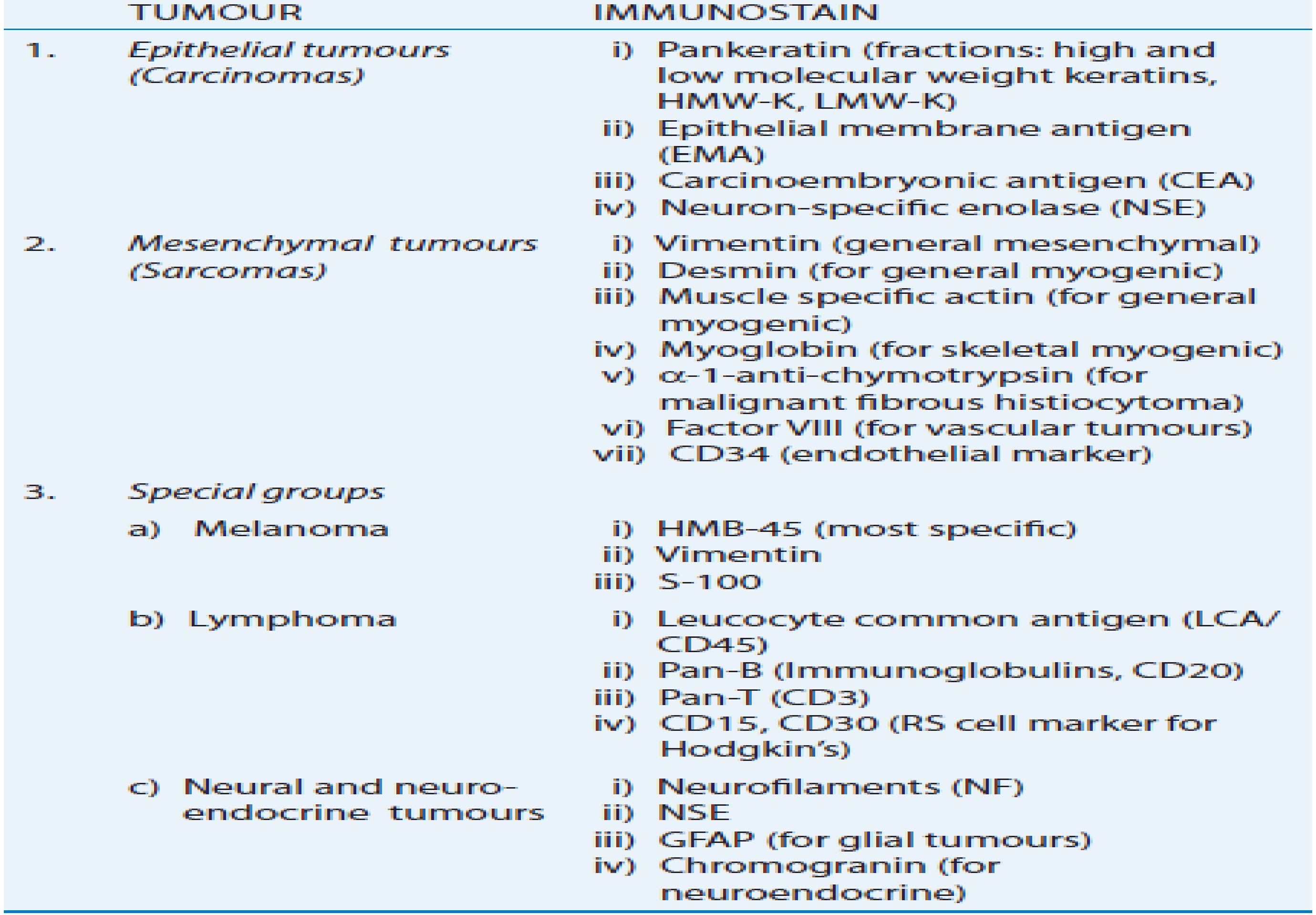
**New Molecular markers**

Dr. PRIYANKA SACHDEV

**An undifferentiated malignant tumour on immunohistochemical stain shows cytoplasmic positivity of most of the tumor cells for cytokeratin. The most probable diagnosis of the tumor is-**

a) Sarcoma
b) Lymphoma
c) Carcinoma
d) Malignant Melanoma

# c



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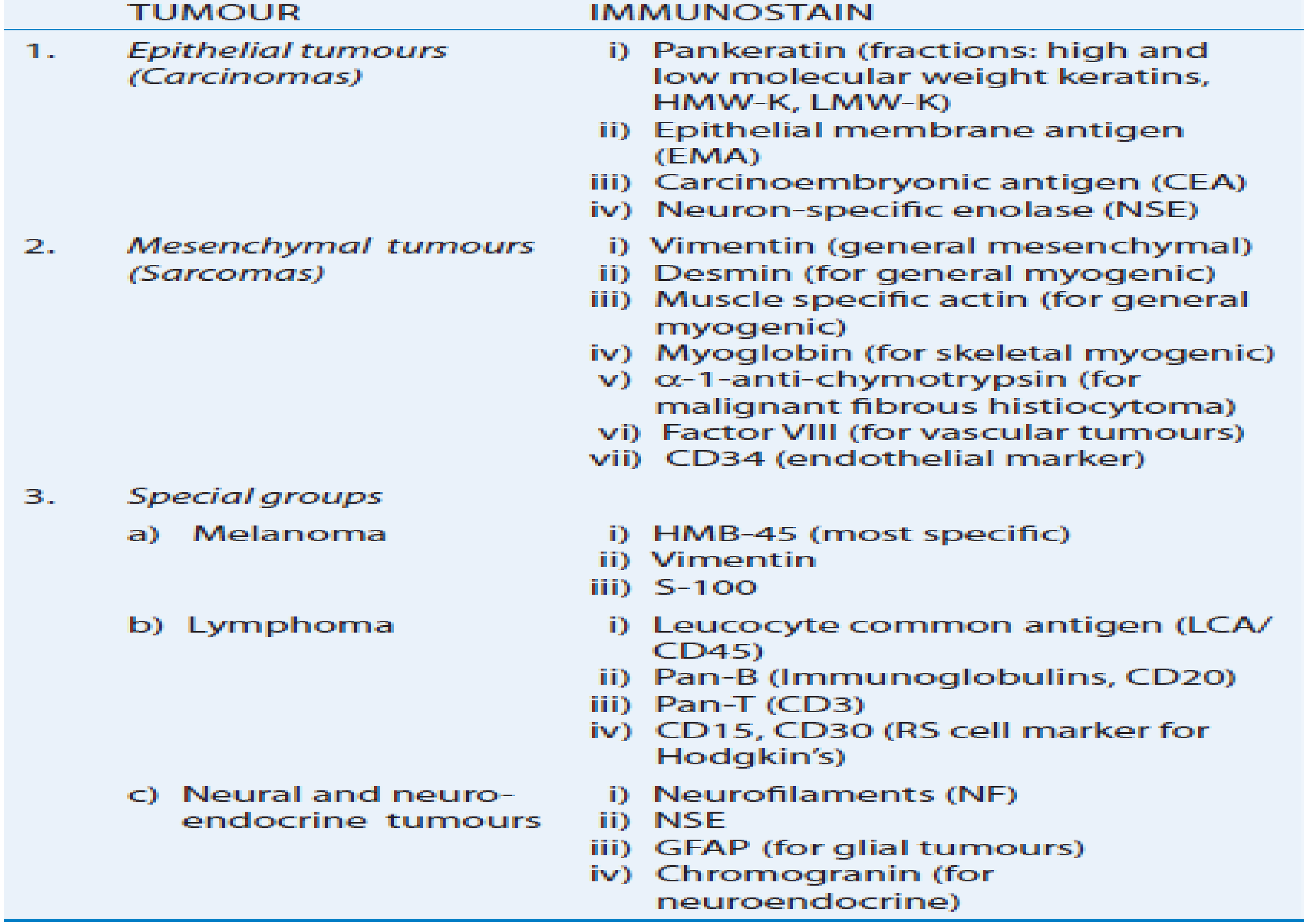
| | c) Neural and neuro-endocrine tumours | i) Neurofilaments (NF)<br>ii) NSE<br>iii) GFAP (for glial tumours)<br>iv) Chromogranin (for neuroendocrine) |

**All of the following pairs of antigens and tumors are correctly matched except-**

a) Vimentin in sarcoma
b) Desmin in carcinoma
c) S100 protein in melanoma
d) Leukocyte common antigen in lymphoma

Dr. PRIYA

# B



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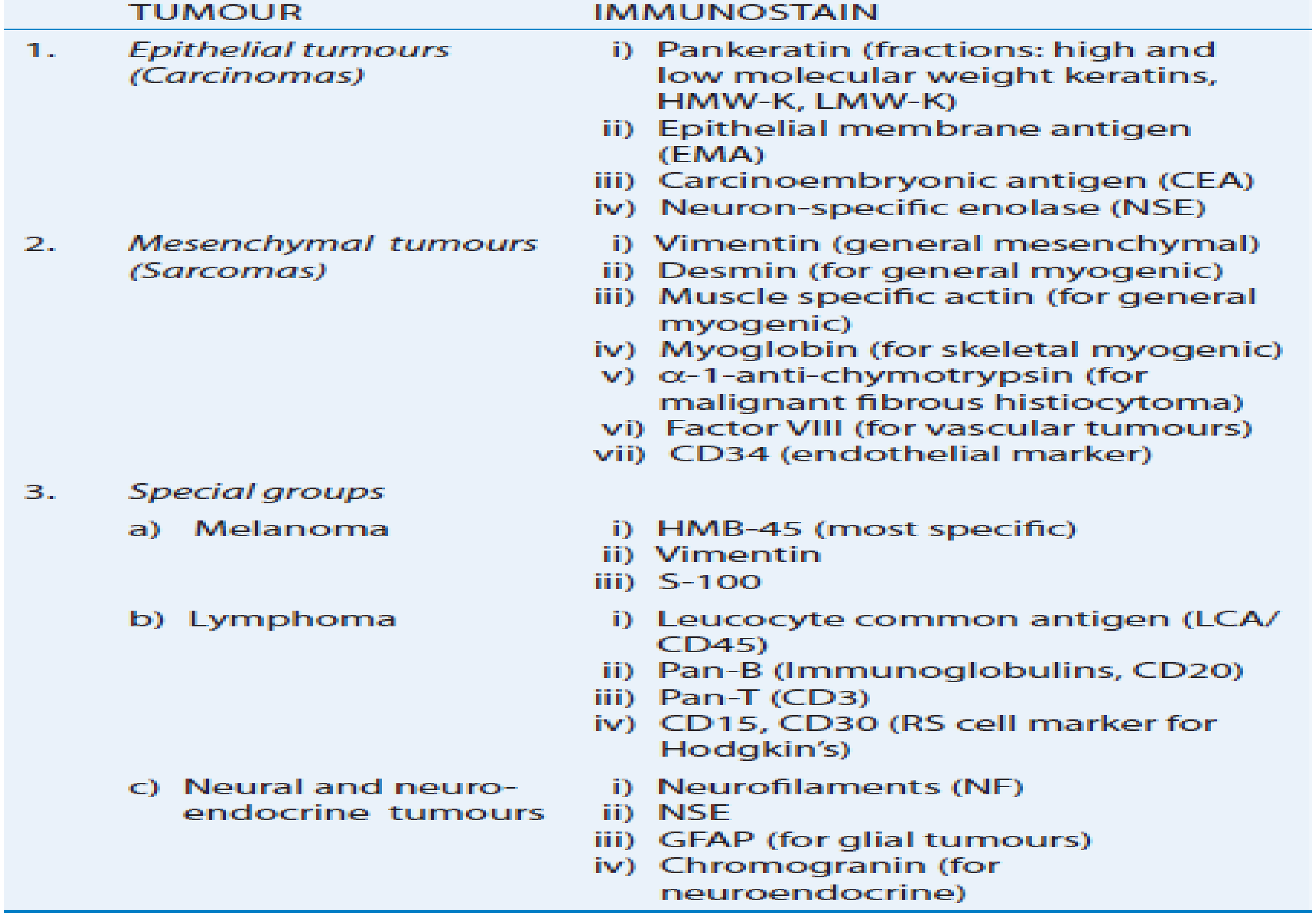
**Squamous cell carcinoma marker is -**

a) Vimentin
b) Cytokeratin
c) Desmin
d) Myogenin

# B



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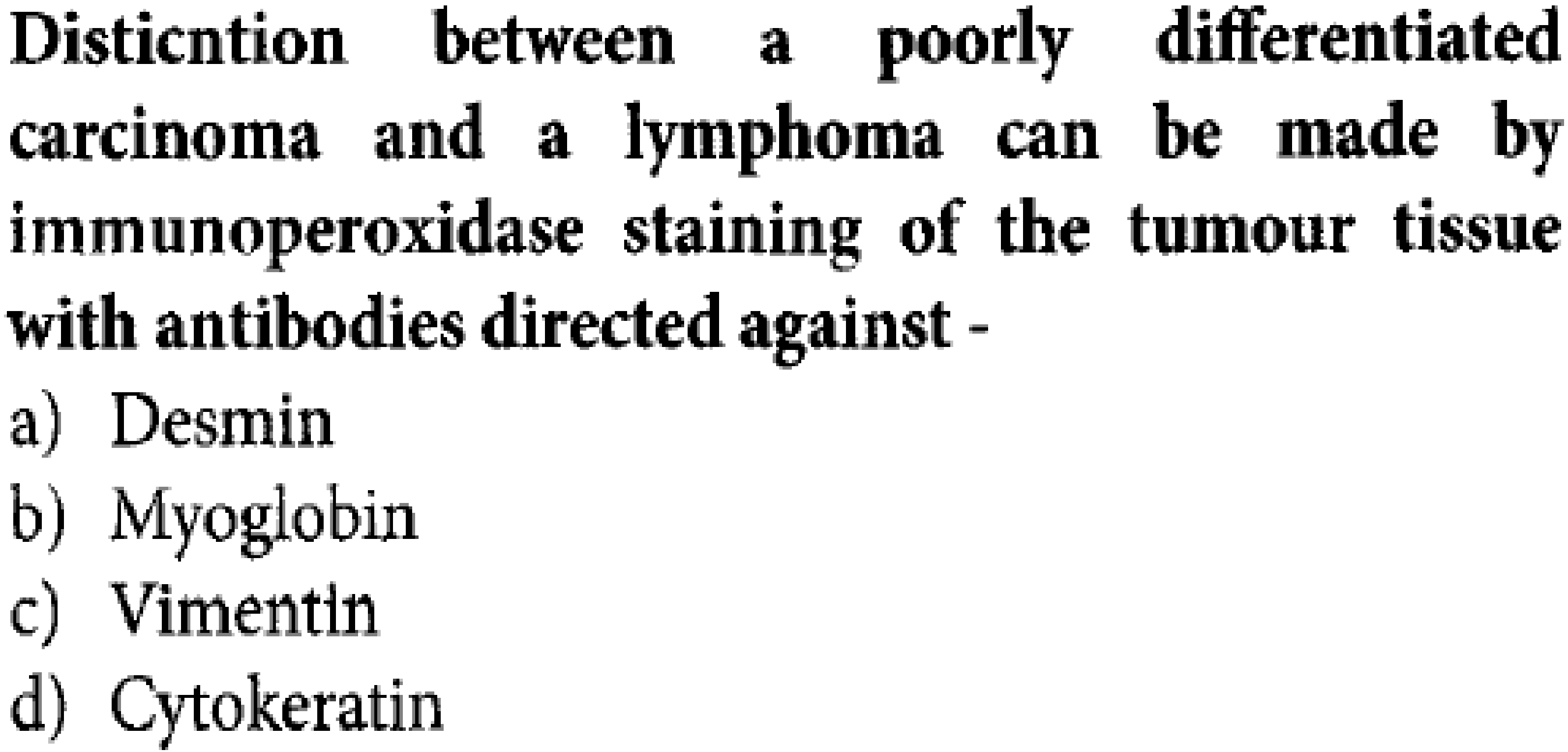
**Dr. PRIYANKA SACHDEV**



**Disticntion between a poorly differentiated carcinoma and a lymphoma can be made by immunoperoxidase staining of the tumour tissue with antibodies directed against -**

a) Desmin
b) Myoglobin
c) Vimentin
d) Cytokeratin

# D

# Thank you for being awake

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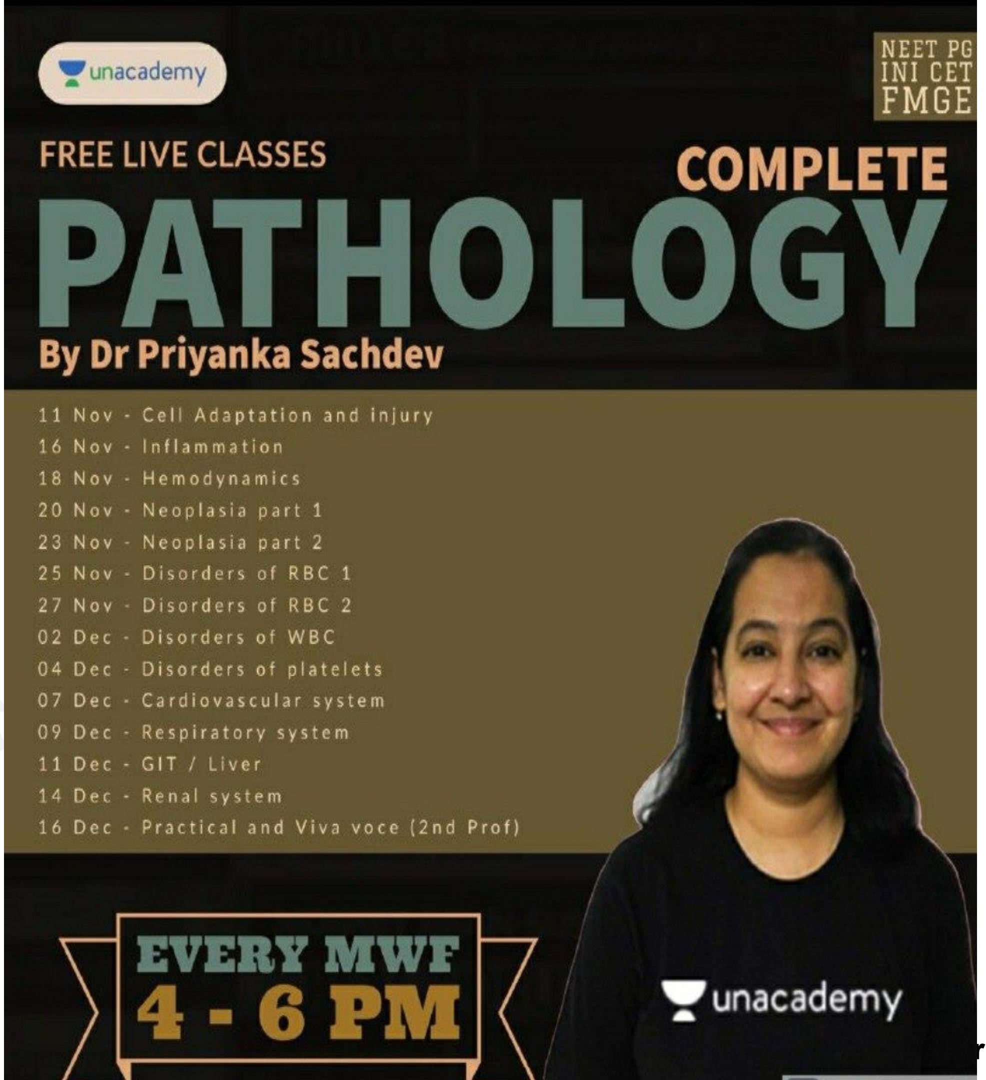
# PHARMACOLOGY

By Dr Priyanka Sachdev

10 Nov - Pharmacokinetics part 1
17 Nov - Pharmacokinetics part 2
19 Nov - Pharmacodynamics
21 Nov - ANS part 1
24 Nov - ANS part 2
26 Nov - ANS part 3
28 Nov - Drugs for Asthma
01 Dec - Oral Hypoglycaemic Agents and Insulin
03 Dec - CNS - Sedatives and hypnotics, Alcohol
05 Dec - CNS - Anti Parkinson's drug
08 Dec - Drugs affecting RAS
10 Dec - Anti-angina and Heart failure drugs
12 Dec - Diuretics, Antidiuretics
15 Dec - Antimicrobials part 1
17 Dec - Antimicrobials part 2

EVERY TTS
4 - 6 PM



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# COMPLETE PATHOLOGY

By Dr Priyanka Sachdev

11 Nov - Cell Adaptation and injury
16 Nov - Inflammation
18 Nov - Hemodynamics
20 Nov - Neoplasia part 1
23 Nov - Neoplasia part 2
25 Nov - Disorders of RBC 1
27 Nov - Disorders of RBC 2
02 Dec - Disorders of WBC
04 Dec - Disorders of platelets
07 Dec - Cardiovascular system
09 Dec - Respiratory system
11 Dec - GIT / Liver
14 Dec - Renal system
16 Dec - Practical and Viva voce (2nd Prof)

**EVERY MWF**
**4 - 6 PM**

Dr

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